

Gliclazide

From Wikipedia, the free encyclopedia

[Jump to navigation](#)[Jump to search](#)

Not to be confused with [glipizide](#) or [glyburide](#).

Gliclazide	
  Gliclazide 30/60 mg (SR) + Metformin 500 mg (SR) + Pioglitazone 15 mg	
Clinical data	
<u>Trade names</u>	Diamicon, others [ⓘ]
<u>AHFS/Drugs.com</u>	Micromedex Detailed Consumer Information
<u>Pregnancy category</u>	AU: <u>C</u>
<u>ATC code</u>	A10BB09 (WHO)
Legal status	
<u>Legal status</u>	AU: <u>S4</u> (Prescription only)
<u>Pharmacokinetic data</u>	
<u>Elimination half-life</u>	10.4 hours
Identifiers	
<u>IUPAC name</u> ^[show]	
<u>CAS Number</u>	21187-98-4 ✓

PubChem CID	3475
DrugBank	DB01120 ✓
ChemSpider	3356 ✓
UNII	G4PX8C4HKV
KEGG	D01599 ✓
ChEBI	CHEBI:31654 ✓
ChEMBL	ChEMBL427216 ✓
CompTox	DTXSID9023095 ✎
Dashboard (EPA)	
ECHA InfoCard	100.040.221 ✎
Chemical and physical data	
Formula	C ₁₅ H ₂₁ N ₃ O ₃ S
Molar mass	323.412 g/mol g·mol ⁻¹
3D model (JSmol)	Interactive image
SMILES [show]	
InChI [show]	
(verify)	

Gliclazide, sold under the brand name **Diamicron** among others, is an [anti-diabetic medication](#) used to treat [diabetes mellitus type 2](#).^[2] It is used when dietary changes, exercise, and weight loss are not enough.^[3] It is taken by mouth.^[2]

Side effect may include [low blood sugar](#), vomiting, [abdominal pain](#), rash, and [liver problems](#).^{[3][2]} Use by those with significant [kidney problems](#), liver problems, or who are [pregnant](#) is not recommended.^{[2][3]} Gliclazide is in the [sulfonylurea](#) family of medications.^[2] It works mostly by increasing the release of [insulin](#).^[2]

Gliclazide was patented in 1966 and approved for medical use in 1972.^[4] It is on the [World Health Organization's List of Essential Medicines](#), the most effective and safe medicines needed in a [health system](#).^[5] The wholesale cost in the [developing world](#) is about US\$2.46–3.92 per month.^[6] In the United Kingdom a month of medication costs the [NHS](#) about 2.12 pounds.^[2] It is not available for sale in the United States.^[2]



Contents

- 1Medical uses
- 2Contraindications
- 3Adverse effects

- [4Interactions](#)
- [5Overdose](#)
- [6Mechanism of action](#)
- [7Properties](#)
- [8Metabolism](#)
- [9References](#)
- [10External links](#)

Medical uses[\[edit\]](#)

Gliclazide is used for control of hyperglycemia in gliclazide-responsive [diabetes mellitus](#) of stable, mild, non-[ketosis](#) prone, type 2 diabetes. It is used when diabetes cannot be controlled by proper dietary management and exercise or when insulin therapy is not appropriate.^[*citation needed*] National Kidney Foundation (2012 Update) claims that Gliclazide does not require dosage uptitration even in end stage kidney disease.

Contraindications[\[edit\]](#)

- Type 1 diabetes^[*citation needed*]
- Hypersensitivity to [sulfonyleureas](#)^[*citation needed*]
- Severe renal or hepatic failure^[*citation needed*] (But relatively useful in mild renal impairment e.g. CKD stage 3)
- Pregnancy and lactation^[*citation needed*]

Adverse effects[\[edit\]](#)

- [Hypoglycemia](#) - while it was shown to have the same efficacy as glimepiride, one of the newer sulfonyleureas, the European GUIDE study has shown that it has approximately 50% less hypoglycaemic confirmed episodes in comparison with glimepiride.^[*!*]

Interactions[\[edit\]](#)

Hyperglycemic action may be caused by [danazol](#), [chlorpromazine](#), [glucocorticoids](#), [progestogens](#), or β -2 agonists. Its hypoglycemic action may be potentiated by [phenylbutazone](#), alcohol, [fluconazole](#), β -blockers, and possibly [ACE inhibitors](#). It has been found that rifampin increases gliclazide metabolism in humans in vivo.^[*!*]

Overdose[\[edit\]](#)

Gliclazide overdose may cause severe hypoglycemia, requiring urgent administration of glucose by IV and monitoring.^[*citation needed*]

Mechanism of action[\[edit\]](#)

Gliclazide selectively binds to sulfonyleurea receptors (SUR-1) on the surface of the pancreatic beta-cells. It was shown to provide cardiovascular protection as it does not bind to sulfonyleurea receptors (SUR-2A) in the heart.^[*!*] This binding effectively closes the K⁺ ion channels. This decreases the efflux of potassium from the cell which leads to the depolarization of the cell. This causes voltage dependent Ca⁺⁺ ion channels to open increasing the Ca⁺⁺ influx. The calcium can then bind to and activate calmodulin which in turn leads to exocytosis of insulin vesicles leading to insulin release.^[*citation*]

- cells but not rat heart or arterial smooth muscle cells". *Diabetologia*. **44** (8): 1019–25. doi:10.1007/s001250100595. PMID 11484080.
11. [^] Urbanova, J.; et al. (2015). "Half-Life of Sulfonylureas in HNF1A and HNF4A Human MODY Patients is not Prolonged as Suggested by the Mouse *Hnf1a*^{-/-} Model". *Current Pharmaceutical Design*. **21**: 5736–5748. doi:10.2174/1381612821666151008124036.
 12. [^] Ballagi-Pordány, György; Köszegehy, Anna; Koltai, Mária-Zsófia; Aranyi, Zoltán; Pogátsa, Gábor (1990). "Divergent cardiac effects of the first and second generation hypoglycemic sulfonylurea compounds". *Diabetes Research and Clinical Practice*. **8** (2): 109–14. doi:10.1016/0168-8227(90)90020-T. PMID 2106423.
 13. [^] Shimoyama, Tatsuhiro; Yamaguchi, Shinya; Takahashi, Kazuto; Katsuta, Hidenori; Ito, Eisuke; Seki, Hiroyuki; Ushikawa, Kenji; Katahira, Hiroshi; et al. (2006). "Gliclazide protects 3T3L1 adipocytes against insulin resistance induced by hydrogen peroxide with restoration of GLUT4 translocation". *Metabolism*. **55** (6): 722–30. doi:10.1016/j.metabol.2006.01.019. PMID 16713429.
 14. [^] Karmoker J, Priya R, Sarkar S, Islam S (2017). "Comparative in vitro equivalence evaluation of some local Gliclazide brands of Bangladesh" (PDF). *The Pharma Innovation Journal*. **6**: 152–157. Retrieved 2018-01-23.
 15. [^] Gopal Venkatesh Shavi et al. Enhanced dissolution and bioavailability of gliclazide using solid dispersion techniques; *International Journal of Drug Delivery* 2 (2010) 49-57
 16. [^] Rieutord, A; Stupans, I; Shenfield, GM; Gross, AS (1995). "Gliclazide hydroxylation by rat liver microsomes". *Xenobiotica*. **25** (12): 1345–54. doi:10.3109/00498259509061922. PMID 8719909.
 17. [^] Elliot, David J.; Lewis, Benjamin C.; Gillam, Elizabeth M. J.; Birkett, Donald J.; Gross, Annette S.; Miners, John O.; Miners, JO (2007). "Identification of the human cytochromes P450 catalysing the rate-limiting pathways of gliclazide elimination". *British Journal of Clinical Pharmacology*. **64** (4): 450–7. doi:10.1111/j.1365-2125.2007.02943.x. PMC 2048545. PMID 17517049.
 18. [^] Zhang, Yifan; Si, Dayong; Chen, Xiaoyan; Lin, Nan; Guo, Yingjie; Zhou, Hui; Zhong, Dafang (2007). "Influence of CYP2C9 and CYP2C19 genetic polymorphisms on pharmacokinetics of gliclazide MR in Chinese subjects". *British Journal of Clinical Pharmacology*. **64** (1): 67–74. doi:10.1111/j.1365-2125.2007.02846.x. PMC 2000619. PMID 17298483.
 19. [^] Xu, H; Williams, K M; Liauw, W S; Murray, M; Day, R O; McLachlan, A J (2009). "Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide". *British Journal of Pharmacology*. **153** (7): 1579–86. doi:10.1038/sj.bjp.0707685. PMC 2437900. PMID 18204476.

Metformin

From Wikipedia, the free encyclopedia
[Jump to navigation](#)[Jump to search](#)

Metformin	
 <p>Carryl[®] MP 30/60 Glucophage 30/60 mg (SR) + Metformin 500 mg (SR) + Pioglitazone 15 mg</p>	
Clinical data	
Pronunciation	<i>/metˈfɔːrmin/</i> , <i>met-FOR-min</i>
<u>Trade names</u>	Glucophage, other
Synonyms	<i>N,N</i> -dimethylbiguanide ^[1]
<u>AHFS/Drugs.com</u>	<u>Monograph</u>
<u>MedlinePlus</u>	<u>a696005</u>
<u>License data</u>	EU <u>EMA</u> : <u>by INN</u> US <u>FDA</u> : <u>metformin</u>
<u>Pregnancy</u>	AU: <u>C</u>

<u>category</u>	US: B (No risk in non-human studies)
<u>Routes of administration</u>	by mouth
<u>ATC code</u>	A10BA02 (WHO)
Legal status	
<u>Legal status</u>	AU: S4 (Prescription only) CA: R-only UK: POM (Prescription only) US: R-only
Pharmacokinetic data	
<u>Bioavailability</u>	50–60% ^{[2][3]}
<u>Protein binding</u>	Minimal ^[2]
<u>Metabolism</u>	Not by liver ^[2]
<u>Elimination half-life</u>	4–8.7 hours ^[2]
<u>Excretion</u>	Urine (90%) ^[2]
Identifiers	
<u>IUPAC name</u> [show]	
<u>CAS Number</u>	657-24-9 ✓
<u>PubChem CID</u>	4091
<u>IUPHAR/BPS</u>	4779
<u>DrugBank</u>	DB00331
<u>ChemSpider</u>	3949 ✓
<u>UNII</u>	9100L32L2N hydrochloride: 786Z46389E
<u>KEGG</u>	D04966 ✓
<u>ChEBI</u>	CHEBI:6801 ✓
<u>ChEMBL</u>	ChEMBL1431 ✓
<u>CompTox</u>	DTXSID2023270 ✎
<u>Dashboard</u> (EPA)	
<u>ECHA InfoCard</u>	100.010.472 ✎

Chemical and physical data	
Formula	C ₄ H ₁₁ N ₅
Molar mass	129.16364 g/mol g·mol ⁻¹
3D model (JSmol)	Interactive image
Density	1.3±0.1 ^[4] g/cm ³
SMILES [show]	
InChI [show]	

Metformin, marketed under the trade name **Glucophage** among others, is the [first-line](#) medication for the treatment of [type 2 diabetes](#),^{[5][6]} particularly in people who are [overweight](#).^[7] It is also used in the treatment of [polycystic ovary syndrome](#).^[5] It is not associated with weight gain.^[8] It is taken by mouth.^[5]

Metformin is generally well tolerated.^[9] Common side effects include [diarrhea](#), [nausea](#), and abdominal pain.^[5] It has a low risk of causing [low blood sugar](#).^[5] [High blood lactic acid level](#) is a concern if the medication is prescribed inappropriately or in overly large doses.^[10] It should not be used in those with significant [liver disease](#) or [kidney problems](#).^[5] While no clear harm comes from use during [pregnancy](#), insulin is generally preferred for [gestational diabetes](#).^{[5][11]} Metformin is a [biguanide](#) antihyperglycemic agent.^[5] It works by decreasing [glucose production](#) by the [liver](#) and increasing the insulin sensitivity of body tissues.^[5]

Metformin was discovered in 1922.^[12] French physician Jean Sterne began study in humans in the 1950s.^[12] It was introduced as a medication in France in 1957 and the United States in 1995.^{[5][13]} Metformin is on the [World Health Organization's List of Essential Medicines](#), which lists the most effective and safe medicines needed in a [health system](#).^[14] Metformin is the most widely used medication for diabetes taken by mouth.^[12] It is available as a [generic medication](#).^[5] The wholesale price in the [developed world](#) was between US\$0.21 and \$5.55 per month as of 2014.^[15] In the United States, it costs US\$5 to US\$25 per month.^[5] In 2016, it was the fourth-most prescribed medication in the United States, with more than 81 million prescriptions.^[16]



Contents

- [1 Medical uses](#)
 - [1.1 Type 2 diabetes](#)
 - [1.2 Polycystic ovarian syndrome](#)
 - [1.3 Diabetes mellitus and pregnancy](#)
 - [1.4 Weight gain](#)
 - [1.5 Use with insulin](#)
- [2 Contraindications](#)
- [3 Adverse effects](#)
 - [3.1 Gastrointestinal](#)
 - [3.2 Lactic acidosis](#)
 - [3.3 Overdose](#)
 - [3.4 Interactions](#)
- [4 Mechanism of action](#)

- 5Chemistry
- 6Pharmacokinetics
- 7History
- 8Society and culture
 - 8.1Environmental
 - 8.2Formulations
- 9Research
- 10See also
- 11References
- 12External links

Medical uses[edit]

Metformin is used to lower the blood sugar in those with type 2 diabetes; it is also used as a second line agent for [infertility](#) in those with polycystic ovary syndrome.^{[5][17]}

Type 2 diabetes[edit]

The [American Diabetes Association](#) and the [American College of Physicians](#) each recommend metformin as a first-line agent to treat type 2 diabetes.^{[18][19][20]} It is as effective as [repaglinide](#) and more effective than all other oral diabetes mellitus type 2 drugs.^[21]

Efficacy[edit]

The UK Prospective Diabetes Study, a large clinical trial performed in 1980–90s, provided evidence that metformin reduced the rate of adverse [cardiovascular](#) outcomes in overweight patients with type 2 diabetes relative to other antihyperglycemic agents.^[22] However, accumulated evidence from other and more recent trials reduced confidence in the efficacy of metformin for cardiovascular disease prevention.^{[23][24]} Outcomes are improved even in those with some degree of kidney disease, [heart failure](#), or [chronic liver disease](#).^[25]

Treatment guidelines for major professional associations including the [European Association for the Study of Diabetes](#), the European Society for Cardiology, and the [American Diabetes Association](#), now describe evidence for the cardiovascular benefits of metformin as equivocal.^{[19][26]}

In 2017, the American College of Physicians's guidelines were updated to recognize metformin as the first-line treatment for type 2 diabetes. These guidelines supersede earlier reviews. For example, a 2014 review found tentative evidence that people treated with sulfonylureas had a higher risk of severe low blood sugar events (RR 5.64), though their risk of nonfatal cardiovascular events was lower than the risk of those treated with metformin (RR 0.67). Not enough data were available at that time to determine the relative risk of death or of death from heart disease.^[27]

Metformin has little or no effect on body weight in type 2 diabetes compared with [placebo](#),^[28] in contrast to sulfonylureas which are associated with weight gain.^[28] There is some evidence that metformin is associated with weight loss in obesity in the absence of diabetes.^{[29][30]} Metformin has a lower risk of [hypoglycemia](#) than the sulfonylureas,^{[31][32]} although hypoglycemia has uncommonly occurred during intense exercise, calorie deficit, or when used with other agents to lower blood glucose.^{[33][34]} Metformin modestly reduces [LDL](#) and [triglyceride](#) levels.^{[31][32]}

Polycystic ovarian syndrome[edit]

In those with [polycystic ovarian syndrome](#) (PCOS), tentative evidence shows that metformin use increases the rate of live births.^[35] This includes in those who have not been able to get pregnant with clomiphene.^[36] Metformin does not appear to change the risk of miscarriage.^[35] A number of other benefits have also been found both during pregnancy and in nonpregnant people with PCOS.^{[37][38]} In women with PCOS undergoing *in vitro* fertilization, evidence does not support a benefit with respect

to live births.^[39] The evidence does not support general use during pregnancy for improving maternal and infant outcomes in obese women.^[40]

The United Kingdom's [National Institute for Health and Clinical Excellence](#) recommended in 2004 that women with PCOS and a [body mass index](#) above 25 be given metformin for [anovulation](#) and [infertility](#) when other therapies fail to produce results.^[41] UK and international [clinical practice guidelines](#) do not recommend metformin as a first-line treatment^[42] or do not recommend it at all, except for women with [glucose intolerance](#).^[43] The guidelines suggest clomiphene as the first medication option and emphasize lifestyle modification independently from medical treatment. Metformin treatment decreases the risk of developing type 2 diabetes mellitus in women with PCOS who exhibited impaired glucose tolerance (IGT) at baseline.^{[44][45]}

Diabetes mellitus and pregnancy^[edit]

A review of metformin use during pregnancy compared to insulin alone found good short-term safety for both the mother and baby, but unclear long-term safety.^[46] Several [observational studies](#) and randomized, controlled trials found metformin to be as effective and safe as insulin for the management of gestational diabetes.^{[47][48]} Nonetheless, several concerns have been raised and evidence on the long-term safety of metformin for both mother and child is lacking.^[49] Compared with insulin, women with gestational diabetes treated with metformin gain less weight and are less likely to develop pre-eclampsia during pregnancy.^{[60][49]} Babies born to women treated with metformin have less [visceral fat](#), and this may make them less prone to insulin resistance in later life.^[51]

Weight gain^[edit] [Gliclazide 30/60 mg \(SR\)+ Metformin 500 mg \(SR\)+](#)

Metformin appears to be safe and effective in counteracting the weight gain caused by the [antipsychotic](#) medications [olanzapine](#) and [clozapine](#).^{[52][53]} Although modest reversal of clozapine-associated weight gain is found with metformin, primary prevention of weight gain is more valuable.^[54]

Use with insulin^[edit]

Metformin may reduce the insulin requirement in [type 1 diabetes](#), albeit with an increased risk of hypoglycemia.^[55]

Contraindications^[edit]

The FDA most recently revised its [prescribing information](#) on metformin in 2016.^[56] Current advice is that metformin is [contraindicated](#) in people with 1) severe renal impairment (estimated [glomerular filtration rate](#) (eGFR) below 30 ml/min/1.73 m²); 2) known hypersensitivity to metformin; or 3) acute or chronic [metabolic acidosis](#), including [diabetic ketoacidosis](#), with or without [coma](#). Warnings are also given regarding the use of metformin in less severe renal impairment, people aged 65 years old or greater, [hypoxic](#) states (e.g., [acute congestive heart failure](#)), excessive alcohol intake, [hepatic impairment](#), concomitant use of certain drugs (e.g. [carbonic anhydrase inhibitors](#) such as [topiramate](#)), surgery, and other procedures, or in people having a radiological study with administration of an [iodinated contrast](#) agent.

Metformin is recommended to be temporarily discontinued before any procedure involving use of iodinated contrast agents, (such as a contrast-enhanced [CT scan](#) or [angiogram](#)) due to the increased risk of lactic acidosis resulting from impaired renal function;^{[57][58]} metformin can be resumed after two days after contrast administration, if renal function is adequate and stable.

Adverse effects^[edit]

The most common [adverse effect](#) of metformin is gastrointestinal irritation, including [diarrhea](#), cramps, nausea, vomiting, and increased [flatulence](#); metformin is more commonly associated with

gastrointestinal side effects than most other antidiabetic medications.^[32] The most serious potential side effect of metformin use is [lactic acidosis](#); this complication is very rare, and the vast majority of these cases seem to be related to comorbid conditions, such as impaired liver or kidney function, rather than to the metformin itself.^[59]

Gastrointestinal^[edit]

Gastrointestinal upset can cause severe discomfort; it is most common when metformin is first administered, or when the dose is increased. The discomfort can often be avoided by beginning at a low dose (1.0 to 1.7 grams per day) and increasing the dose gradually, but even with low doses, 5% of people may be unable to tolerate metformin.^[60] Use of slow- or extended-release preparations may improve tolerability.^[60]

Long-term use of metformin has been associated with increased [homocysteine](#) levels^[61] and [malabsorption](#) of [vitamin B₁₂](#).^{[62][63]} Higher doses and prolonged use are associated with increased incidence of [vitamin B₁₂ deficiency](#),^[64] and some researchers recommend screening or prevention strategies.^[65]

Lactic acidosis^[edit]

[Lactic acidosis](#) almost never occurs with metformin exposure during routine medical care.^[66] Rates of metformin-associated lactic acidosis is about nine per 100,000 person-years, which is similar to the background rate of lactic acidosis in the general population.^[67] A systematic review concluded no data exists to definitively link metformin to lactic acidosis.^[68]

Metformin is generally safe in people with mild to moderate chronic kidney disease, with proportional reduction of metformin dose according to severity of estimated glomerular filtration rate and with periodic assessment of kidney function, (e.g., periodic plasma creatinine measurement).^[69] The [FDA](#) recommends avoiding the use of metformin in more severe chronic kidney disease, below the [estimated glomerular filtration rate](#) (eGFR) cutoff of 30 mL/minute/1.73 m².^[70] Lactate uptake by the liver is diminished with metformin use because lactate is a [substrate](#) for hepatic [gluconeogenesis](#), a process that metformin inhibits. In healthy individuals, this slight excess is cleared by other mechanisms (including uptake by unimpaired kidneys), and no significant elevation in blood levels of lactate occurs.^[31] Given severely-impaired kidney function, clearance of metformin and lactate is reduced, increasing levels of both, and possibly causing lactic acid buildup. Because metformin decreases liver uptake of lactate, any condition that may precipitate lactic acidosis is a contraindication. Common causes include [alcoholism](#) (due to depletion of [NAD⁺](#) stores), heart failure and respiratory disease (due to inadequate tissue oxygenation); the most common cause is kidney disease.^[71]

Metformin has been suggested as increasing production of lactate in the large intestine, which could potentially contribute to lactic acidosis in those with risk factors.^[72] However, the clinical significance of this is unknown, and the risk of metformin-associated lactic acidosis is most commonly attributed to decreased hepatic uptake rather than increased intestinal production.^{[31][71][73]}

The risk of metformin-associated lactic acidosis is also increased by massive overdose of metformin, although even quite large doses are often not fatal.^[74]

Overdose^[edit]

The most common symptoms following overdose include vomiting, [diarrhea](#), abdominal pain, [tachycardia](#), drowsiness, and, rarely, [hypoglycemia](#) or [hyperglycemia](#).^{[75][76]} Treatment of metformin overdose is generally supportive, as no specific antidote is known. Extracorporeal treatments are recommended in severe overdoses.^[77] Due to metformin's low [molecular weight](#) and lack of [plasma protein binding](#), these techniques have the benefit of removing metformin from [blood plasma](#), preventing further lactate overproduction.^[77]

Metformin may be quantified in blood, plasma, or serum to monitor therapy, confirm a diagnosis of poisoning, or assist in a forensic death investigation. Blood or plasma metformin concentrations are usually in a range of 1–4 mg/l in persons receiving therapeutic doses, 40–120 mg/l in victims of acute overdosage, and 80–200 mg/l in fatalities. Chromatographic techniques are commonly employed.^{[78][79]}

Interactions^[edit]

The [H₂-receptor antagonist cimetidine](#) causes an increase in the plasma concentration of metformin by reducing [clearance](#) of metformin by the kidneys;^[80] both metformin and cimetidine are cleared from the body by [tubular secretion](#), and both, particularly the [cationic](#) (positively [charged](#)) form of cimetidine, may compete for the same transport mechanism.^[81] A small [double-blind](#), randomized study found the [antibiotic cephalixin](#) to also increase metformin concentrations by a similar mechanism;^[82] theoretically, other cationic medications may produce the same effect.^[81]

Metformin also interacts with [anticholinergic](#) medications, due to their effect on gastric motility. Anticholinergic drugs reduce gastric motility, prolonging the time drugs spend in the [gastrointestinal tract](#). This impairment may lead to more metformin being absorbed than without the presence of an anticholinergic drug, thereby increasing the concentration of metformin in the plasma and increasing the risk for adverse effects.^[83]

Mechanism of action^[edit]

The molecular mechanism of metformin is incompletely understood. Multiple potential mechanisms of action have been proposed: inhibition of the mitochondrial respiratory chain (complex I), activation of [AMP-activated protein kinase](#) (AMPK), inhibition of glucagon-induced elevation of [cyclic adenosine monophosphate](#) (cAMP) with reduced activation of [protein kinase A](#) (PKA), inhibition of mitochondrial [glycerophosphate dehydrogenase](#), and an effect on [gut microbiota](#).^{[84][85][86]} Ultimately, it decreases gluconeogenesis (liver glucose production).^[72] It also has an insulin-sensitizing effect with multiple actions on tissues including the liver, skeletal muscle, endothelium, adipose tissue, and the ovary.^{[44][87]} The average patient with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one-third.^[88]

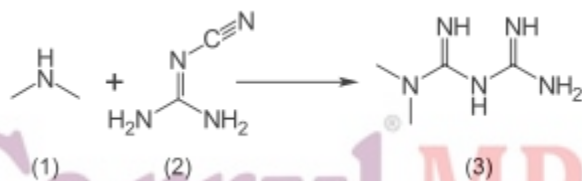
Activation of [AMPK](#) was required for metformin's inhibitory effect on liver glucose production.^[89] AMPK is an enzyme that plays an important role in insulin signalling, whole body energy balance and the metabolism of glucose and [fats](#).^[90] AMPK Activation was required for an increase in the expression of [small heterodimer partner](#), which in turn inhibited the [expression](#) of the hepatic gluconeogenic genes [phosphoenolpyruvate carboxykinase](#) and [glucose 6-phosphatase](#).^[91] Metformin is frequently used in research along with [AICA ribonucleotide](#) as an AMPK agonist. The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, metformin increases the concentration of [cytosolic adenosine monophosphate](#) (AMP) (as opposed to a change in total AMP or total AMP/[adenosine triphosphate](#)).^[92] Increased cellular AMP has been proposed to explain the inhibition of glucagon-induced increase in cAMP and activation of PKA.^[84] Metformin and other biguanides may antagonize the action of [glucagon](#), thus reducing fasting glucose levels.^[93] Metformin also induces a profound shift in the faecal microbial community profile in diabetic mice and this may contribute to its mode of action possibly through an effect on [glucagon-like peptide-1](#) secretion.^[85]

In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral [glucose uptake](#) (by inducing the phosphorylation of [GLUT4](#) enhancer factor), decreases insulin-induced suppression of [fatty acid oxidation](#),^[94] and decreases absorption of glucose from the [gastrointestinal tract](#). Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors.^[95] The increase in insulin binding after metformin treatment has also been demonstrated in patients with [NIDDM](#).^[96]

AMPK probably also plays a role in increased peripheral insulin sensitivity, as metformin administration increases AMPK activity in skeletal muscle.^[97] AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. Some metabolic actions of metformin do appear to occur by AMPK-independent mechanisms.

Chemistry^[edit]

Metformin hydrochloride (1,1-dimethylbiguanide hydrochloride) is freely-soluble in water, slightly soluble in ethanol, but almost insoluble in acetone, ether, or chloroform. The pKa of metformin is 12.4.^[98] The usual [synthesis](#) of metformin, originally described in 1922, involves the one-pot reaction of [dimethylamine hydrochloride](#) and [2-cyanoguanidine](#) over heat.^{[99][100]}



According to the procedure described in the 1975 Aron patent,^[101] and the *Pharmaceutical Manufacturing Encyclopedia*,^[102] [equimolar](#) amounts of dimethylamine and 2-cyanoguanidine are dissolved in [toluene](#) with cooling to make a [concentrated](#) solution, and an equimolar amount of [hydrogen chloride](#) is slowly added. The mixture begins to boil on its own, and after cooling, metformin hydrochloride [precipitates](#) with a 96% [yield](#).

Pharmacokinetics^[edit]

Metformin has an oral [bioavailability](#) of 50–60% under [fasting](#) conditions, and is absorbed slowly.^{[81][103]} Peak plasma concentrations (C_{max}) are reached within one to three hours of taking immediate-release metformin and four to eight hours with extended-release formulations.^{[81][103]} The [plasma protein binding](#) of metformin is negligible, as reflected by its very high [apparent volume of distribution](#) (300–1000 l after a single dose). [Steady state](#) is usually reached in one or two days.^[81]

Metformin has acid dissociation constant values (pKa) of 2.8 and 11.5, so exists very largely as the hydrophilic cationic species at physiological pH values. The metformin pKa values make metformin a stronger base than most other basic medications with less than 0.01% nonionized in blood. Furthermore, the [lipid solubility](#) of the nonionized species is slight as shown by its low logP value (log(10) of the distribution coefficient of the nonionized form between octanol and water) of −1.43. These chemical parameters indicate low lipophilicity and, consequently, rapid passive diffusion of metformin through cell membranes is unlikely. As a result of its low lipid solubility it requires the [transporter SLC22A1](#) in order for it to enter cells.^{[104][105]} The logP of metformin is less than that of [phenformin](#) (−0.84) because two methyl substituents on metformin impart lesser lipophilicity than the larger phenylethyl side chain in [phenformin](#). More lipophilic derivatives of metformin are presently under investigation with the aim of producing prodrugs with superior oral absorption than metformin.^[106]

Metformin is not [metabolized](#). It is [cleared](#) from the body by [tubular secretion](#) and excreted unchanged in the urine; metformin is undetectable in blood plasma within 24 hours of a single oral dose.^{[81][107]} The average [elimination half-life](#) in plasma is 6.2 hours.^[81] Metformin is distributed to (and appears to accumulate in) [red blood cells](#), with a much longer elimination half-life: 17.6 hours^[81] (reported as ranging from 18.5 to 31.5 hours in a single-dose study of nondiabetics).^[107]

History^[edit]



Galega officinalis, a natural source of galegine

The [biguanide](#) class of antidiabetic medications, which also includes the withdrawn agents [phenformin](#) and [buformin](#), originates from the [French lilac](#) or goat's rue (*Galega officinalis*), a plant used in folk medicine for several centuries.^[108]

Metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of *N,N*-dimethylguanidine.^[99] In 1929, Slotta and Tschesche discovered its sugar-lowering action in rabbits, finding it the most potent biguanide analog they studied.^[109] This result was completely forgotten, as other [guanidine](#) analogs, such as the [synthalins](#), took over and were themselves soon overshadowed by insulin.^[110]

Interest in metformin resumed at the end of the 1940s. In 1950, metformin, unlike some other similar compounds, was found not to decrease [blood pressure](#) and [heart rate](#) in animals.^[111] That year, Filipino physician Eusebio Y. Garcia^[112] used metformin (he named it Fluamine) to treat influenza; he noted the medication "lowered the blood sugar to minimum physiological limit" and was not toxic. Garcia believed metformin to have [bacteriostatic](#), [antiviral](#), [antimalarial](#), [antipyretic](#) and [analgesic](#) actions.^[113] In a series of articles in 1954, Polish pharmacologist Janusz Supniewski^[114] was unable to confirm most of these effects, including lowered blood sugar. Instead he observed antiviral effects in humans.^{[115][116]}

French diabetologist Jean Sterne studied the antihyperglycemic properties of [galegine](#), an [alkaloid](#) isolated from *Galega officinalis*, which is related in structure to metformin and had seen brief use as an antidiabetic before the synthalins were developed.^[117] Later, working at Laboratoires Aron in Paris, he was prompted by Garcia's report to reinvestigate the blood sugar-lowering activity of metformin and several biguanide analogs. Sterne was the first to try metformin on humans for the treatment of diabetes; he coined the name "Glucophage" (glucose eater) for the medication and published his results in 1957.^{[119][117]}

Metformin became available in the [British National Formulary](#) in 1958. It was sold in the UK by a small Aron subsidiary called Rona.^[118]

Broad interest in metformin was not rekindled until the withdrawal of the other biguanides in the 1970s. Metformin was approved in Canada in 1972,^[119] but did not receive approval by the U.S. [Food and Drug Administration](#) (FDA) for type 2 diabetes until 1994.^[120] Produced under license by [Bristol-Myers Squibb](#), Glucophage was the first branded formulation of metformin to be marketed in the U.S., beginning on March 3, 1995.^[121] [Generic](#) formulations are now available in several countries,

and metformin is believed to have become the world's most widely prescribed antidiabetic medication.^[117]

Society and culture^[edit]

Environmental^[edit]

Metformin and its major transformation product guanylurea are present in wastewater treatment plant effluents and regularly detected in surface waters. Guanylurea concentrations above 200 µg L⁻¹ have been measured in a German river which are amongst the highest reported for pharmaceutical transformation products in aquatic environments.^[122]

Formulations^[edit]



Generic metformin 500-mg tablets, as sold in the United Kingdom

The name "Metformin" is the [BAN](#), [USAN](#) and [INN](#) for the medication. It is sold under several [trade names](#), including Glucophage XR, Carbophage SR, Riomet, Fortamet, Glumetza, Obimet, Gluformin, Dianben, Diabex, Diaformin, Siofor, Metfogamma and Glifor.

Liquid metformin is sold under the name Riomet in India. Each 5 ml of Riomet is equivalent to the 500-mg tablet form.^[123]

Metformin IR (immediate release) is available in 500, 850, and 1000-mg tablets. All of these are available as generic medications in the U.S.

Metformin SR (slow release) or XR (extended release) was introduced in 2004. It is available in 500, 750, and 1000-mg strengths, mainly to counteract common gastrointestinal side effects, as well as to increase compliance by reducing [pill burden](#). No difference in effectiveness exists between the two preparations.

Combination with other medications^[edit]

When used for type 2 diabetes, metformin is often prescribed in combination with other medications.

Several are available as [fixed-dose combinations](#), to reduce pill burden and simplify administration.^[124]

Thiazolidinediones (glitazones)^[edit]

Rosiglitazone^[edit]

A combination of metformin and [rosiglitazone](#) was released in 2002 and sold as Avandamet by [GlaxoSmithKline](#).^[125]

By 2009 it had become the most popular metformin combination.^[126]

In 2005, the stock of Avandamet was removed from the market, after inspections showed the factory where it was produced was violating [good manufacturing practices](#).^[127] The medication pair continued to be prescribed separately and Avandamet was again available by the end of that year. A generic formulation of metformin/rosiglitazone from [Teva](#) received tentative approval from the FDA and reached the market in early 2012.^[128]

However, following a [meta-analysis](#) in 2007 that linked the medication's use to an increased risk of [heart attack](#),^[129] concerns were raised over the safety of medicines containing rosiglitazone. In September 2010 the [European Medicines Agency](#) (EMA) recommended that the medication be suspended from the European market because the benefits of rosiglitazone no longer outweighed the risks.^{[130][131]}

It was withdrawn from the market in the UK and India in 2010,^[132] and in New Zealand and South Africa in 2011.^[133] From November 2011 until November 2013 the FDA^[134] did not allow rosiglitazone or metformin/rosiglitazone to be sold without a prescription; moreover, makers were required to notify patients of the risks associated with its use, and the drug had to be purchased by mail order through specified pharmacies.^[135]

In November 2013, the FDA lifted its earlier restrictions on rosiglitazone after reviewing the results of the 2009 RECORD clinical trial (a six-year, open label [randomized control trial](#)), which failed to show elevated risk of heart attack or death associated with the medication.^{[136][137][138]}

Pioglitazone[\[edit\]](#)

The combination of metformin and [pioglitazone](#) (Actoplus Met, Piomet, Politor) remains available in U.S. and Europe.^{[139][140]}

DPP-4 inhibitors[\[edit\]](#)

[Dipeptidyl peptidase-4 inhibitors](#) inhibit [dipeptidyl peptidase-4](#) and thus reduce [glucagon](#) and blood glucose levels.

DPP-4 inhibitors combined with metformin include a [sitagliptin/metformin](#) combination and a [saxagliptin](#) combination (Komboglyze), and with [alogliptin](#) as Kazano among others.

In Europe, Canada, and elsewhere metformin combined with [linagliptin](#) is marketed under the trade name Jentadueto.^[141]

Sulfonylureas[\[edit\]](#)

[Sulfonylureas](#) act by increasing insulin release from the [beta cells](#) in the [pancreas](#). Metformin is available combined with the sulfonylureas [glipizide](#) (Metaglip) and [glibenclamide](#)(US: glyburide) (Glucovance).

Generic formulations of metformin/glipizide and metformin/glibenclamide are available (the latter is more popular).^[142]

Meglitinide[\[edit\]](#)

[Meglitinides](#) are similar to [sulfonylureas](#).

A [repaglinide](#)/metformin combination is sold as Prandimet.

Triple combination[\[edit\]](#)

The combination of metformin with pioglitazone and glibenclamide^[143] is available in India as Triformin.

Research[\[edit\]](#)

Metformin has been studied for its effects on multiple other conditions, including:

- [Non-alcoholic fatty liver disease](#).^{[144][145][146]}
- [Premature puberty](#).^{[146][147]}
- [Cancer](#).^{[148][149]}
- [Cardiovascular disease](#) in people with diabetes.^[150]
- Aging (*C. elegans* and crickets).^[105] A 2017 review found that people with diabetes who were taking metformin had lower all-cause mortality. They also had reduced cancer and cardiovascular disease compared with those on other therapies.^[150] As of 2016 it is being studied to see what effect it may have on aging.^[151]

See also[[edit](#)]

- [List of drugs](#)



[Pharmacy and pharmacology portal](#)



[Medicine portal](#)

References[[edit](#)]

1. [^] [Sirtori CR, Franceschini G, Galli-Kienle M, Cighetti G, Galli G, Bondioli A, Conti F \(December 1978\). "Disposition of metformin \(N,N-dimethylbiguanide\) in man". *Clinical Pharmacology and Therapeutics*. **24** \(6\): 683–93. doi:10.1002/cpt1978246683. PMID 710026.](#)
2. [^] [Jump up to:^{a b c d e} Dunn CJ, Peters DH \(May 1995\). "Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus". *Drugs*. **49** \(5\): 721–49. doi:10.2165/00003495-199549050-00007. PMID 7601013.](#)
3. [^] [Hundal RS, Inzucchi SE \(2003\). "Metformin: new understandings, new uses". *Drugs*. **63**\(18\): 1879–94. doi:10.2165/00003495-200363180-00001. PMID 12930161.](#)
4. [^] ["metformin msds".](#)
5. [^] [Jump up to:^{a b c d e f g h i j k l m} "Metformin Hydrochloride". *The American Society of Health-System Pharmacists*. Archived from the original on 24 December 2016. Retrieved 2 January 2017.](#)
6. [^] [Maruthur NM, Tseng E, Hutflless S, Wilson LM, Suarez-Cuervo C, Berger Z, Chu Y, Iyoha E, Segal JB, Bolen S \(June 2016\). "Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis". *Annals of Internal Medicine*. **164** \(11\): 740–51. doi:10.7326/M15-2650. PMID 27088241.](#)
7. [^] [Clinical Obesity \(2nd ed.\). Oxford: John Wiley & Sons. 2008. p. 262. ISBN 978-0-470-98708-7. Archived from the original on 2017-09-08.](#)
8. [^] ["Type 2 diabetes and metformin. First choice for monotherapy: weak evidence of efficacy but well-known and acceptable adverse effects". *Prescrire International*. **23** \(154\): 269–72. November 2014. PMID 25954799.](#)
9. [^] [Triggle CR, Ding H \(January 2017\). "Metformin is not just an antihyperglycaemic drug but also has protective effects on the vascular endothelium". *Acta Physiologica*. **219** \(1\): 138–151. doi:10.1111/apha.12644. PMID 26680745.](#)
10. [^] [Lipska KJ, Bailey CJ, Inzucchi SE \(June 2011\). "Use of metformin in the setting of mild-to-moderate renal insufficiency". *Diabetes Care*. **34** \(6\): 1431–7. doi:10.2337/dc10-2361. PMC 3114336. PMID 21617112.](#)
11. [^] [Lautatzis ME, Goulis DG, Vrontakis M \(November 2013\). "Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review". *Metabolism*. **62** \(11\): 1522–34. doi:10.1016/j.metabol.2013.06.006. PMID 23886298.](#)
12. [^] [Jump up to:^{a b c} Fischer, Janos \(2010\). *Analogue-based Drug Discovery II*. John Wiley & Sons. p. 49. ISBN 978-3-527-63212-1. Archived from the original on 2017-09-08.](#)
13. [^] [McKee, Mitchell Bebel Stargrove, Jonathan Treasure, Dwight L. \(2008\). *Herb, nutrient, and drug interactions : clinical implications and therapeutic strategies*. St. Louis, Mo.: Mosby/Elsevier. p. 217. ISBN 978-0-323-02964-3. Archived from the original on 2017-09-08.](#)

14. [^ "WHO Model List of Essential Medicines \(19th List\)" \(PDF\)](#). World Health Organization. April 2015. [Archived](#) (PDF) from the original on 13 December 2016. Retrieved 8 December 2016.
15. [^ "Metformin"](#). [Archived](#) from the original on 3 August 2017. Retrieved 11 January 2016.
16. [^ "The Top 300 of 2019"](#). [clincalc.com](#). Retrieved 22 December 2018.
17. [^ Lord JM, Flight IH, Norman RJ \(October 2003\). "Metformin in polycystic ovary syndrome: systematic review and meta-analysis"](#). *BMJ*. **327** (7421): 951–3. [doi:10.1136/bmj.327.7421.951](#). [PMC 259161](#). [PMID 14576245](#).
18. [^ Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, Marinopoulos SS, Puhan MA, Ranasinghe P, Block L, Nicholson WK, Hutfless S, Bass EB, Bolen S \(May 2011\). "Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations"](#). *Annals of Internal Medicine*. **154** (9): 602–13. [doi:10.7326/0003-4819-154-9-201105030-00336](#). [PMC 3733115](#). [PMID 21403054](#).
19. [^ Jump up to:^a Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR \(June 2012\). "Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association \(ADA\) and the European Association for the Study of Diabetes \(EASD\)"](#). *Diabetes Care*. **35** (6): 1364–79. [doi:10.2337/dc12-0413](#). [PMC 3357214](#). [PMID 22517736](#).
20. [^ Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P \(February 2012\). "Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians"](#). *Annals of Internal Medicine*. **156** (3): 218–31. [doi:10.7326/0003-4819-156-3-201202070-00011](#). [PMID 22312141](#).
21. [^ Jia Y, Lao Y, Zhu H, Li N, Leung SW \(January 2019\). "Is metformin still the most efficacious first-line oral hypoglycaemic drug in treating type 2 diabetes? A network meta-analysis of randomized controlled trials"](#). *Obes Rev*. **20** (1): 1–12. [doi:10.1111/obr.12753](#). [PMID 30230172](#).
22. [^ "Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes \(UKPDS 34\)"](#). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. **352** (9131): 854–65. September 1998. [doi:10.1016/S0140-6736\(98\)07037-8](#). [PMID 9742977](#).
23. [^ Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, Feldman L, Vassy J, Wilson R, Bass EB, Brancati FL \(October 2008\). "Cardiovascular outcomes in trials of oral diabetes medications: a systematic review"](#). *Archives of Internal Medicine*. **168** (19): 2070–80. [doi:10.1001/archinte.168.19.2070](#). [PMC 2765722](#). [PMID 18955635](#).
24. [^ Boussageon R, Supper I, Bejan-Angoulvant T, Kellou N, Cucherat M, Boissel JP, Kassai B, Moreau A, Gueyffier F, Cornu C \(2012\). "Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials"](#). *PLoS Medicine*. **9** (4): e1001204. [doi:10.1371/journal.pmed.1001204](#). [PMC 3323508](#). [PMID 22509138](#).
25. [^ Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, Wang X, Tang S, Nagi A, Kosinski AS, Williams JW \(February 2017\). "Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review"](#). *Annals of Internal Medicine*. **166** (3): 191–200. [doi:10.7326/M16-1901](#). [PMC 5293600](#). [PMID 28055049](#).
26. [^ Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskiran MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL \(May 2014\). "ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD—summary"](#). *Diabetes & Vascular Disease Research*. **11** (3): 133–73. [doi:10.1177/1479164114525548](#). [PMID 24800783](#).
27. [^ Hemmingsen B, Schroll JB, Wetterslev J, Gluud C, Vaag A, Sonne DP, Lundstrøm LH, Almdal T \(July 2014\). "Sulfonylurea versus metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized clinical trials and trial sequential analysis"](#). *CMAJ Open*. **2** (3): E162–75. [doi:10.9778/cmajo.20130073](#). [PMC 4185978](#). [PMID 25295236](#).
28. [^ Jump up to:^a Johansen, K. \(1999\). "Efficacy of metformin in the treatment of NIDDM. Meta-analysis"](#). *Diabetes Care*. **22** (1): 33–37. [doi:10.2337/diacare.22.1.33](#). [ISSN 0149-5992](#).
29. [^ Golay A \(January 2008\). "Metformin and body weight"](#). *International Journal of Obesity*. **32** (1): 61–72. [doi:10.1038/sj.ijo.0803695](#). [PMID 17653063](#).
30. [^ Mead E, Atkinson G, Richter B, Metzendorf MI, Baur L, Finer N, Corpeleijn E, O'Malley C, Ells LJ \(November 2016\). "Drug interventions for the treatment of obesity in children and adolescents"](#). *The*

Cochrane Database of Systematic Reviews. 11:

CD012436. doi:10.1002/14651858.CD012436. hdl:10149/620651. PMID 27899001.

31. ^ Jump up to:^{a b c d} Maharani U (2009). "Chapter 27: Diabetes Mellitus & Hypoglycemia". In Papadakis MA, McPhee SJ (eds.). *Current Medical Diagnosis and Treatment 2010* (49th ed.). McGraw-Hill Medical. pp. 1092–93. ISBN 978-0-07-162444-2.
32. ^ Jump up to:^{a b c} Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB, Brancati FL (September 2007). "Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus". *Annals of Internal Medicine*. **147** (6): 386–99. doi:10.7326/0003-4819-147-6-200709180-00178. PMID 17638715.
33. ^ DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM (2005). *Pharmacotherapy: a pathophysiologic approach*. New York: McGraw-Hill. ISBN 978-0-07-141613-9.
34. ^ "Glucophage package insert". Princeton, NJ: Bristol-Myers Squibb Company; 2009.
35. ^ Jump up to:^{a b} Morley, LC; Tang, T; Yasmin, E; Norman, RJ; Balen, AH (29 November 2017). "Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility". *The Cochrane Database of Systematic Reviews*. 11: CD003053. doi:10.1002/14651858.CD003053.pub6. PMID 29183107. Our updated review suggests that metformin alone may be beneficial over placebo for live birth, although the evidence quality was low.
36. ^ Ghazeeri GS, Nassar AH, Younes Z, Awwad JT (June 2012). "Pregnancy outcomes and the effect of metformin treatment in women with polycystic ovary syndrome: an overview". *Acta Obstetrica et Gynecologica Scandinavica*. **91** (6): 658–78. doi:10.1111/j.1600-0412.2012.01385.x. PMID 22375613.
37. ^ Kumar P, Khan K (May 2012). "Effects of metformin use in pregnant patients with polycystic ovary syndrome". *Journal of Human Reproductive Sciences*. **5** (2): 166–9. doi:10.4103/0974-1208.101012. PMC 3493830. PMID 23162354.
38. ^ Tay, CT; Joham, AE; Hiam, DS; Gadalla, MA; Pundir, J; Thangaratnam, S; Teede, HJ; Moran, LJ (November 2018). "Pharmacological and surgical treatment of nonreproductive outcomes in polycystic ovary syndrome: An overview of systematic reviews". *Clinical Endocrinology*. **89** (5): 535–553. doi:10.1111/cen.13753. PMID 29846959.
39. ^ Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Macedo CR (November 2014). "Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome". *Cochrane Database Syst Rev* (11): CD006105. doi:10.1002/14651858.CD006105.pub3. PMID 25406011.
40. ^ Dodd JM, Grivell RM, Deussen AR, Hague WM (July 2018). "Metformin for women who are overweight or obese during pregnancy for improving maternal and infant outcomes". *Cochrane Database Syst Rev*. 7: CD010564. doi:10.1002/14651858.CD010564.pub2. PMID 30039871.
41. ^ National Collaborating Centre for Women's and Children's Health (2004). *Fertility: assessment and treatment for people with fertility problems* (PDF). London: Royal College of Obstetricians and Gynaecologists. pp. 58–59. ISBN 978-1-900364-97-3. Archived (PDF) from the original on 2009-07-11.
42. ^ Balen A (December 2008). "Metformin therapy for the management of infertility in women with polycystic ovary syndrome" (PDF). *Scientific Advisory Committee Opinion Paper 13*. Royal College of Obstetricians and Gynaecologists. Archived from the original (PDF) on 2009-12-18. Retrieved 2009-12-13.
43. ^ The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (March 2008). "Consensus on infertility treatment related to polycystic ovary syndrome". *Human Reproduction*. **23** (3): 462–77. doi:10.1093/humrep/dem426. PMID 18308833.
44. ^ Jump up to:^{a b} Diamanti-Kandarakis E, Economou F, Palimeri S, Christakou C (September 2010). "Metformin in polycystic ovary syndrome". *Annals of the New York Academy of Sciences*. **1205** (1): 192–8. Bibcode:2010NYASA1205..192D. doi:10.1111/j.1749-6632.2010.05679.x. PMID 20840272.
45. ^ Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN (February 2010). "Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome". *European Journal of Endocrinology*. **162**(2): 193–212. doi:10.1530/EJE-09-0733. PMID 19841045.
46. ^ Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L (January 2017). "Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis". *Diabetic Medicine*. **34** (1): 27–36. doi:10.1111/dme.13150. PMID 27150509.
47. ^ Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E (January 2009). "Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic

- review". *Obstetrics and Gynecology*. **113** (1): 193–205. doi:10.1097/AOG.0b013e318190a459. PMID 19104375.
48. [^] Kitwitee P, Limwattananon S, Limwattananon C, Waleekachonlert O, Ratanachotpanich T, Phimpilai M, Nguyen TV, Pongchaiyakul C (September 2015). "Metformin for the treatment of gestational diabetes: An updated meta-analysis". *Diabetes Research and Clinical Practice*. **109** (3): 521–32. doi:10.1016/j.diabres.2015.05.017. PMID 26117686.
49. [^] Jump up to:^a [^] Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R (January 2015). "Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis". *BMJ (Systematic Review & Meta-Analysis)*. **350**: h102. doi:10.1136/bmj.h102. PMC 4301599. PMID 25609400.
50. [^] Alqudah A, McKinley MC, McNally R, Graham U, Watson CJ, Lyons TJ, McClements L (February 2018). "Risk of pre-eclampsia in women taking metformin: a systematic review and meta-analysis". *Diabet. Med.* **35** (2): 160–172. doi:10.1111/dme.13523. PMID 29044702.
51. [^] Sivalingam VN, Myers J, Nicholas S, Balen AH, Crosbie EJ (2014). "Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications". *Human Reproduction Update*. **20** (6): 853–68. doi:10.1093/humupd/dmu037. PMID 25013215.
52. [^] Choi YJ (2015). "Efficacy of adjunctive treatments added to olanzapine or clozapine for weight control in patients with schizophrenia: a systematic review and meta-analysis". *TheScientificWorldJournal*. **2015**: 1–10. doi:10.1155/2015/970730. PMC 4310265. PMID 25664341.
53. [^] Praharaj SK, Jana AK, Goyal N, Sinha VK (March 2011). "Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis". *British Journal of Clinical Pharmacology*. **71** (3): 377–82. doi:10.1111/j.1365-2125.2010.03783.x. PMC 3045546. PMID 21284696.
54. [^] Siskind DJ, Leung J, Russell AW, Wysoczanski D, Kisely S (2016). "Metformin for Clozapine Associated Obesity: A Systematic Review and Meta-Analysis". *PLOS One*. **11**(6): e0156208. Bibcode:2016PLoSO..1156208S. doi:10.1371/journal.pone.0156208. PMC 4909277. PMID 27304831.
55. [^] Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR (May 2010). "The use of metformin in type 1 diabetes: a systematic review of efficacy". *Diabetologia*. **53** (5): 809–20. doi:10.1007/s00125-009-1636-9. PMID 20057994.
56. [^] Research, Center for Drug Evaluation and. "Drug Safety and Availability - FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function". www.fda.gov. Retrieved 2018-12-18.
57. [^] Weir J (March 19, 1999). "Guidelines with Regard to Metformin-Induced Lactic Acidosis and X-ray Contrast Medium Agents". *Royal College of Radiologists*. Retrieved October 26, 2007 through the [Internet Archive](#).
58. [^] Thomsen HS, Morcos SK (August 2003). "Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines". *The British Journal of Radiology*. **76**(908): 513–8. doi:10.1259/bjr/26964464. PMID 12893691.
59. [^] Khurana R, Malik IS (January 2010). "Metformin: safety in cardiac patients". *Heart*. **96**(2): 99–102. doi:10.1136/hrt.2009.173773. PMID 19564648.
60. [^] Jump up to:^a [^] Fujita Y, Inagaki N (January 2017). "Metformin: New Preparations and Nonglycemic Benefits". *Current Diabetes Reports*. **17** (1): 5. doi:10.1007/s11892-017-0829-8. PMID 28116648.
61. [^] Wulffelé MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, Donker AJ, Stehouwer CD (November 2003). "Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial". *Journal of Internal Medicine*. **254** (5): 455–63. doi:10.1046/j.1365-2796.2003.01213.x. PMID 14535967.
62. [^] Andrès E, Noel E, Goichot B (October 2002). "Metformin-associated vitamin B12 deficiency". *Archives of Internal Medicine*. **162** (19): 2251–2. doi:10.1001/archinte.162.19.2251-a. PMID 12390080.
63. [^] Gilligan MA (February 2002). "Metformin and vitamin B12 deficiency". *Archives of Internal Medicine*. **162** (4): 484–5. doi:10.1001/archinte.162.4.484. PMID 11863489.
64. [^] de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD (May 2010). "Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial". *BMJ*. **340**: c2181. doi:10.1136/bmj.c2181. PMC 2874129. PMID 20488910.

65. [^](#) Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM (October 2006). "Risk factors of vitamin B(12) deficiency in patients receiving metformin". *Archives of Internal Medicine*. **166** (18): 1975–9. [doi:10.1001/archinte.166.18.1975](#). [PMID 17030830](#).
66. [^](#) Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B (January 2009). "Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes". *Diabetologia*. **52** (1): 17–30. [doi:10.1007/s00125-008-1157-y](#). [PMID 18941734](#).
67. [^](#) Stang M, Wysowski DK, Butler-Jones D (June 1999). "Incidence of lactic acidosis in metformin users". *Diabetes Care*. **22** (6): 925–7. [doi:10.2337/diacare.22.6.925](#). [PMID 10372243](#).
68. [^](#) Salpeter SR, Greyber E, Pasternak GA, Salpeter EE (November 2003). "Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis". *Archives of Internal Medicine*. **163** (21): 2594–602. [doi:10.1001/archinte.163.21.2594](#). [PMID 14638559](#).
69. [^](#) Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK (2014). "[Metformin in patients with type 2 diabetes and kidney disease: a systematic review](#)". *JAMA*. **312** (24): 2668–75. [doi:10.1001/jama.2014.15298](#). [PMC 4427053](#). [PMID 25536258](#).
70. [^](#) Research, Center for Drug Evaluation and. "[Drug Safety and Availability - FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function](#)". [www.fda.gov](#). FDA. Retrieved 21 December 2018.
71. [^](#) [Jump up to:^{a b}](#) Shu AD, Myers MG, Shoelson SE (2005). "Chapter 29: Pharmacology of the Endocrine Pancreas". In Golan ED, Tashjian AH, Armstrong EJ, Galanter JM, Armstrong AW, Arnaout RA, Rose HS (eds.). *Principles of pharmacology: the pathophysiologic basis of drug therapy*. Philadelphia: Lippincott, Williams & Wilkins. pp. 540–41. [ISBN 978-0-7817-4678-6](#).
72. [^](#) [Jump up to:^{a b}](#) Kirpichnikov D, McFarlane SI, Sowers JR (July 2002). "Metformin: an update". *Annals of Internal Medicine*. **137** (1): 25–33. [doi:10.7326/0003-4819-137-1-200207020-00009](#). [PMID 12093242](#).
73. [^](#) Davis SN (2006). "Chapter 60: Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Pancreas". In Brunton L, Lazo J, Parker K (eds.). [Goodman & Gilman's The Pharmacological Basis of Therapeutics](#) (11th ed.). New York: McGraw-Hill. [ISBN 978-0-07-142280-2](#).
74. [^](#) Teale KF, Devine A, Stewart H, Harper NJ (July 1998). "The management of metformin overdose". *Anaesthesia*. **53** (7): 698–701. [doi:10.1046/j.1365-2044.1998.436-az0549.x](#). [PMID 9771180](#).
75. [^](#) Forrester MB (July 2008). "Adult metformin ingestions reported to Texas poison control centers, 2000-2006". *Human & Experimental Toxicology*. **27** (7): 575–83. [CiteSeerX 10.1.1.1031.9486](#). [doi:10.1177/0960327108090589](#). [PMID 18829734](#).
76. [^](#) Suchard JR, Grotsky TA (August 2008). "[Fatal metformin overdose presenting with progressive hyperglycemia](#)". *The Western Journal of Emergency Medicine*. **9** (3): 160–4. [PMC 2672258](#). [PMID 19561734](#).
77. [^](#) [Jump up to:^{a b}](#) Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, Hoffman RS, Nolin TD, Ghannoum M (August 2015). "Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup". *Critical Care Medicine*. **43** (8): 1716–30. [doi:10.1097/CCM.0000000000001002](#). [PMID 25860205](#).
78. [^](#) Liu A, Coleman SP (November 2009). "Determination of metformin in human plasma using hydrophilic interaction liquid chromatography-tandem mass spectrometry". *Journal of Chromatography B*. **877** (29): 3695–700. [doi:10.1016/j.jchromb.2009.09.020](#). [PMID 19783231](#).
79. [^](#) R. Baselt, *Disposition of Toxic Drugs and Chemicals in Man*, 8th edition, Biomedical Publications, Foster City, CA, 2008, pp. 939–940.
80. [^](#) Somogyi A, Stockley C, Keal J, Rolan P, Bochner F (May 1987). "[Reduction of metformin renal tubular secretion by cimetidine in man](#)". *British Journal of Clinical Pharmacology*. **23** (5): 545–51. [doi:10.1111/j.1365-2125.1987.tb03090.x](#). [PMC 1386190](#). [PMID 3593625](#).
81. [^](#) [Jump up to:^{a b c d e f g h}](#) Bristol-Myers Squibb (August 27, 2008). "[Glucophage \(metformin hydrochloride tablets\) Label Information](#)" (PDF). U.S. Food and Drug Administration. [Archived](#) (PDF) from the original on September 22, 2010. Retrieved 2009-12-08.
82. [^](#) Jayasagar G, Krishna Kumar M, Chandrasekhar K, Madhusudan Rao C, Madhusudan Rao Y (2002). "Effect of cephalixin on the pharmacokinetics of metformin in healthy human

- volunteers". *Drug Metabolism and Drug Interactions*. **19** (1): 41–8. doi:10.1515/dmdi.2002.19.1.41. PMID 12222753.
83. ^ May M, Schindler C (April 2016). "Clinically and pharmacologically relevant interactions of antidiabetic drugs". *Therapeutic Advances in Endocrinology and Metabolism*. **7** (2): 69–83. doi:10.1177/2042018816638050. PMC 4821002. PMID 27092232.
84. ^ Jump up to:^a Rena G, Pearson ER, Sakamoto K (September 2013). "Molecular mechanism of action of metformin: old or new insights?". *Diabetologia*. **56** (9): 1898–906. doi:10.1007/s00125-013-2991-0. PMC 3737434. PMID 23835523.
85. ^ Jump up to:^a Burcelin R (May 2014). "The antidiabetic gutsy role of metformin uncovered?". *Gut*. **63**(5): 706–7. doi:10.1136/gutjnl-2013-305370. PMID 23840042.
86. ^ Madiraju AK, Erion DM, Rahimi Y, Zhang XM, Braddock DT, Albright RA, Prigaro BJ, Wood JL, Bhanot S, MacDonald MJ, Jurczak MJ, Camporez JP, Lee HY, Cline GW, Samuel VT, Kibbey RG, Shulman GI (June 2014). "Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase". *Nature*. **510** (7506): 542–6. Bibcode:2014Natur.510..542M. doi:10.1038/nature13270. PMC 4074244. PMID 24847880.
87. ^ Lord JM, Flight IH, Norman RJ (October 2003). "Metformin in polycystic ovary syndrome: systematic review and meta-analysis". *BMJ*. **327** (7421): 951–3. doi:10.1136/bmj.327.7421.951. PMC 259161. PMID 14576245.
88. ^ Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, Inzucchi SE, Schumann WC, Petersen KF, Landau BR, Shulman GI (December 2000). "Mechanism by which metformin reduces glucose production in type 2 diabetes". *Diabetes*. **49** (12): 2063–9. doi:10.2337/diabetes.49.12.2063. PMC 2995498. PMID 11118008.
89. ^ Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE (October 2001). "Role of AMP-activated protein kinase in mechanism of metformin action". *The Journal of Clinical Investigation*. **108** (8): 1167–74. doi:10.1172/JCI13505. PMC 209533. PMID 11602624.
90. ^ Towler MC, Hardie DG (February 2007). "AMP-activated protein kinase in metabolic control and insulin signaling". *Circulation Research*. **100** (3): 328–41. doi:10.1161/01.RES.0000256090.42690.05. PMID 17307971.
91. ^ Kim YD, Park KG, Lee YS, Park YY, Kim DK, Nedumaran B, Jang WG, Cho WJ, Ha J, Lee IK, Lee CH, Choi HS (February 2008). "Metformin inhibits hepatic gluconeogenesis through AMP-activated protein kinase-dependent regulation of the orphan nuclear receptor SHP". *Diabetes*. **57** (2): 306–14. doi:10.2337/db07-0381. PMID 17909097.
92. ^ Zhang L, He H, Balschi JA (July 2007). "Metformin and phenformin activate AMP-activated protein kinase in the heart by increasing cytosolic AMP concentration". *American Journal of Physiology. Heart and Circulatory Physiology*. **293** (1): H457–66. doi:10.1152/ajpheart.00002.2007. PMID 17369473.
93. ^ Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ (February 2013). "Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP". *Nature*. **494** (7436): 256–60. Bibcode:2013Natur.494..256M. doi:10.1038/nature11808. PMC 3573218. PMID 23292513.
94. ^ Collier CA, Bruce CR, Smith AC, Lopaschuk G, Dyck DJ (July 2006). "Metformin counters the insulin-induced suppression of fatty acid oxidation and stimulation of triacylglycerol storage in rodent skeletal muscle". *American Journal of Physiology. Endocrinology and Metabolism*. **291** (1): E182–9. doi:10.1152/ajpendo.00272.2005. PMID 16478780.
95. ^ Bailey CJ, Turner RC (February 1996). "Metformin". *The New England Journal of Medicine*. **334** (9): 574–9. doi:10.1056/NEJM199602293340906. PMID 8569826.
96. ^ Fantus IG, Brosseau R (October 1986). "Mechanism of action of metformin: insulin receptor and postreceptor effects in vitro and in vivo". *The Journal of Clinical Endocrinology and Metabolism*. **63** (4): 898–905. doi:10.1210/jcem-63-4-898. PMID 3745404.
97. ^ Musi N, Hirshman MF, Nygren J, Svanfeldt M, Bavenholm P, Rooyackers O, Zhou G, Williamson JM, Ljunqvist O, Efendic S, Moller DE, Thorell A, Goodyear LJ (July 2002). "Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes". *Diabetes*. **51** (7): 2074–81. doi:10.2337/diabetes.51.7.2074. PMID 12086935.
98. ^ Tilley, Jefferson, Joseph Grimsby, Shawn Erickson, and Steven Berthel. "Diabetes Drugs: Present and Emerging." *Burger's Medicinal Chemistry and Drug Discovery* (2003): 1-38.
99. ^ Jump up to:^a Werner E, Bell J (1922). "The preparation of methylguanidine, and of ββ-dimethylguanidine by the interaction of dicyandiamide, and methylammonium and dimethylammonium chlorides respectively". *J. Chem. Soc., Trans*. **121**: 1790–95. doi:10.1039/CT9222101790.

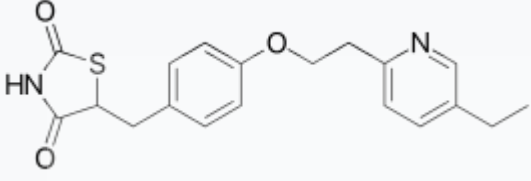
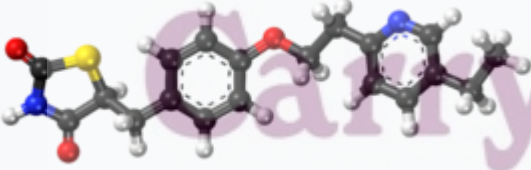
100. [^ Shapiro SL, Parrino VA, Freedman L \(1959\). "Hypoglycemic Agents. I Chemical Properties of \$\beta\$ -Phenethylbiguanide. A New Hypoglycemic Agent". *J Am Chem Soc.* **81** \(9\): 2220–25. doi:10.1021/ja01518a052.](#)
101. [^ "Procédé de préparation de chlorhydrate de diméthylbiguanide". Patent FR 2322860 \(in French\). 1975.](#)
102. [^ *Pharmaceutical Manufacturing Encyclopedia \(Sittig's Pharmaceutical Manufacturing Encyclopedia\)*. **3** \(3rd ed.\). Norwich, NY: William Andrew. 2007. p. 2208. ISBN 978-0-8155-1526-5.](#)
103. [^ Jump up to:^a ^b Heller JB \(2007\). "*Metformin overdose in dogs and cats*" \(PDF\). *Veterinary Medicine \(April\)*: 231–33. Archived from *the original* \(PDF\) on 2007-10-23.](#)
104. [^ Rosilio C, Ben-Sahra I, Bost F, Peyron JF \(May 2014\). "Metformin: a metabolic disruptor and anti-diabetic drug to target human leukemia". *Cancer Letters*. **346** \(2\): 188–96. doi:10.1016/j.canlet.2014.01.006. PMID 24462823.](#)
105. [^ Jump up to:^a ^b Pryor R, Cabreiro F \(November 2015\). "*Repurposing metformin: an old drug with new tricks in its binding pockets*". *The Biochemical Journal*. **471** \(3\): 307–22. doi:10.1042/bj20150497. PMC 4613459. PMID 26475449.](#)
106. [^ Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong JK, Furlong TJ, Greenfield JR, Greenup LC, Kirkpatrick CM, Ray JE, Timmins P, Williams KM \(February 2011\). "Clinical pharmacokinetics of metformin". *Clinical Pharmacokinetics*. **50** \(2\): 81–98. doi:10.2165/11534750-000000000-00000. PMID 21241070.](#)
107. [^ Jump up to:^a ^b Robert F, Fendri S, Hary L, Lacroix C, Andréjak M, Lalau JD \(June 2003\). "Kinetics of plasma and erythrocyte metformin after acute administration in healthy subjects". *Diabetes & Metabolism*. **29** \(3\): 279–83. doi:10.1016/s1262-3636\(07\)70037-x. PMID 12909816.](#)
108. [^ Witters LA \(October 2001\). "*The blooming of the French lilac*". *The Journal of Clinical Investigation*. **108** \(8\): 1105–7. doi:10.1172/JCI14178. PMC 209536. PMID 11602616.](#)
109. [^ See Chemical Abstracts, v.23, 42772 \(1929\) Slotta KH, Tschesche R \(1929\). "*Uber Biguanide. II. Die Blutzuckersenkende Wirkung der Biguanides*". *Berichte der Deutschen Chemischen Gesellschaft B: Abhandlungen*. **62** \(6\): 1398–1405. doi:10.1002/cber.19290620605.](#)
110. [^ Jump up to:^a ^b Campbell IW \(2007\). Campbell IW \(ed.\). "*Metformin – life begins at 50: A symposium held on the occasion of the 43rd Annual Meeting of the European Association for the Study of Diabetes, Amsterdam, The Netherlands, September 2007*". *The British Journal of Diabetes & Vascular Disease*. **7** \(5\): 247–52. doi:10.1177/14746514070070051001.](#)
111. [^ Dawes GS, Mott JC \(March 1950\). "*Circulatory and respiratory reflexes caused by aromatic guanidines*". *British Journal of Pharmacology and Chemotherapy*. **5** \(1\): 65–76. doi:10.1111/j.1476-5381.1950.tb00578.x. PMC 1509951. PMID 15405470.](#)
112. [^ About Eusebio Y. Garcia, see: Carteciano J \(2005\). "*Search for DOST-NRCP Dr. Eusebio Y. Garcia Award*". *Philippines Department of Science and Technology*. Archived from the original on 2009-10-24. Retrieved 2009-12-05.](#)
113. [^ Quoted from Chemical Abstracts, v.45, 24828 \(1951\) Garcia EY \(1950\). "*Fluamine, a new synthetic analgesic and antifu drug*". *J Philippine Med Assoc*. **26**: 287–93.](#)
114. [^ About Janusz Supniewski, see: Wołkow PP, Korbut R \(April 2006\). "*Pharmacology at the Jagiellonian University in Krakow. short review of contribution to global science and cardiovascular research through 400 years of history*" \(PDF\). *Journal of Physiology and Pharmacology*. **57** Suppl 1: 119–36. PMID 16766803. Archived \(PDF\) from the original on 2009-10-24.](#)
115. [^ See Chemical Abstracts, v. 52, 22272 \(1958\) Supniewski J, Chrusciel T \(1954\). "\[*N*-dimethyl-di-guanide and its biological properties\]". *Archivum Immunologiae et Therapiae Experimentalis \(in Polish\)*. **2**: 1–15. PMID 13269290.](#)
116. [^ Quoted from Chemical Abstracts, v.49, 74699 \(1955\) Supniewski J, Krupinska J \(1954\). "\[*Effect of biguanide derivatives on experimental cowpox in rabbits*\]"'. *Bulletin de l'Academie Polonaise des Sciences, Classe 3: Mathematique, Astronomie, Physique, Chimie, Geologie et Geographie \(in French\)*. **2**\(Classe II\): 161–65.](#)
117. [^ Jump up to:^a ^b ^c Bailey CJ, Day C \(2004\). "*Metformin: its botanical background*". *Practical Diabetes International*. **21** \(3\): 115–17. doi:10.1002/pdi.606. Archived from *the original* on 2012-12-17.](#)
118. [^ Hadden DR \(October 2005\). "*Goat's rue—French lilac—Italian fitch—Spanish sainfoin: gallega officinalis and metformin: the Edinburgh connection*" \(PDF\). *The Journal of the Royal College of Physicians of Edinburgh*. **35** \(3\): 258–60. PMID 16402501.](#)



119. [^](#) Lucis OJ (January 1983). "[The status of metformin in Canada](#)". *Canadian Medical Association Journal*. **128** (1): 24–6. [PMC 1874707](#). [PMID 6847752](#).
120. [^](#) Cruzan SM (December 30, 1994). "[FDA Approves New Diabetes Drug](#)" (Press release). U.S. [Food and Drug Administration](#). Archived from [the original](#) on September 29, 2007. Retrieved 2007-01-06.
121. [^](#) Glucophage Label and Approval History. U.S. [Food and Drug Administration](#). Retrieved January 8, 2007. Data available for download on [FDA website Archived 2009-08-14 at the Wayback Machine](#).
122. [^](#) Posselt M, Jaeger A, Schaper JL, Radke M, Benskin JP (December 2018). "Determination of polar organic micropollutants in surface and pore water by high-resolution sampling-direct injection-ultra high performance liquid chromatography-tandem mass spectrometry". *Environ. Sci.: Process. Impacts*. **20**: 1716–1727. [doi:10.1039/C8EM00390D](#). [PMID 30350841](#).
123. [^](#) "[Metformin](#)". rxwiki. 9 July 2012. [Archived from the original on 15 September 2013](#).
124. [^](#) Bailey CJ, Day C (June 2009). "Fixed-dose single tablet antidiabetic combinations". *Diabetes, Obesity & Metabolism*. **11** (6): 527–33. [doi:10.1111/j.1463-1326.2008.00993.x](#). [PMID 19175373](#).
125. [^](#) "[FDA Approves GlaxoSmithKline's Avandamet \(rosiglitazone maleate and metformin HCl\), The Latest Advancement in the Treatment of Type 2 Diabetes](#)" (Press release). [GlaxoSmithKline](#). October 12, 2002. [Archived from the original on January 21, 2007](#). Retrieved 2006-12-27.
126. [^](#) "[2009 Top 200 branded drugs by total prescriptions](#)" (PDF). Archived from [the original](#) (PDF) on 2011-07-14. (96.5 KB). *Drug Topics* (June 17, 2010). Retrieved September 2, 2010.
127. [^](#) "[Questions and Answers about the Seizure of Paxil CR and Avandamet](#)" (Press release). U.S. [Food and Drug Administration](#). March 4, 2005. Archived from [the original](#) on October 14, 2007. Retrieved 2006-12-27.
128. [^](#) "[Teva Pharm announces settlement of generic Avandia, Avandamet, and Avandaryl litigation with GlaxoSmithKline](#)" (Press release). Reuters. September 27, 2007. Retrieved 2009-02-17.
129. [^](#) Nissen SE, Wolski K (June 2007). "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes". *The New England Journal of Medicine*. **356** (24): 2457–71. [doi:10.1056/NEJMoa072761](#). [PMID 17517853](#).
130. [^](#) "[European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim](#)". News and Events. European Medicines Agency. 2018-09-17. [Archived from the original on 2015-09-24](#).
131. [^](#) "[Call to 'suspend' diabetes drug](#)". BBC News. 2010-09-23. [Archived from the original on 2010-09-24](#).
132. [^](#) "[Drugs banned in India](#)". Central Drugs Standard Control Organization, Dte.GHS, Ministry of Health and Family Welfare, Government of India. Archived from [the original](#) on 2015-02-21. Retrieved 2013-09-17.
133. [^](#) "[Diabetes drug withdrawn](#)". [Stuff.co.nz](#). NZPA. 17 February 2011. Retrieved 5 November 2011.
134. [^](#) Harris G (February 19, 2010). "[Controversial Diabetes Drug Harms Heart, U.S. Concludes](#)". *New York Times*. [Archived from the original on March 19, 2017](#).
135. [^](#) "[Most Popular E-mail Newsletter](#)". USA Today. 2011-05-24.
136. [^](#) "[Glaxo's Avandia Cleared From Sales Restrictions by FDA](#)". Bloomberg. [Archived from the original on 2014-11-09](#).
137. [^](#) U.S. [Food and Drug Administration](#) (November 25, 2013). "[FDA requires removal of certain restrictions on the diabetes drug Avandia](#)". [Archived from the original on May 4, 2015](#).
138. [^](#) "[US agency reverses stance on controversial diabetes drug](#)". [Archived from the original on 2015-12-11](#).
139. [^](#) "[European Medicines Agency – Human medicines – CHMP summary of positive opinion for Pioglitazone ratiopharm](#)". [Archived from the original on 2015-12-11](#).
140. [^](#) "[Safety Information – Actoplus Met \(pioglitazone and metformin\) fixed-dose combination tablets](#)". [Archived from the original on 2015-12-11](#).
141. [^](#) [Jentadueto Archived 2012-07-23 at the Wayback Machine](#) at the European Medicines Agency. First published 25/05/2012

142. [^](#) ["The Use of Medicines in the United States: Review of 2010" \(PDF\)](#). [Archived\(PDF\) from the original on 2011-04-22](#). (1.79 MB). IMS Institute for Healthcare Informatics (April 2011). Retrieved April 28, 2011.
143. [^](#) Panikar V, Chandalia HB, Joshi SR, Fafadia A, Santvana C (November 2003). "Beneficial effects of triple drug combination of pioglitazone with glibenclamide and metformin in type 2 diabetes mellitus patients on insulin therapy". *The Journal of the Association of Physicians of India*. **51**: 1061–4. [PMID 15260389](#).
144. [^](#) Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N (September 2001). "Metformin in non-alcoholic steatohepatitis". *Lancet*. **358** (9285): 893–4. [doi:10.1016/S0140-6736\(01\)06042-1](#). [PMID 11567710](#).
145. [^](#) Socha P, Horvath A, Vajro P, Dziechciarz P, Dhawan A, Szajewska H (May 2009). "Pharmacological interventions for nonalcoholic fatty liver disease in adults and in children: a systematic review". *Journal of Pediatric Gastroenterology and Nutrition*. **48** (5): 587–96. [doi:10.1097/MPG.0b013e31818e04d1](#). [PMID 19412008](#).
146. [^](#) [Jump up to:^a ^b](#) Angelico F, Burattin M, Alessandri C, Del Ben M, Lirussi F (January 2007). "Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis". *The Cochrane Database of Systematic Reviews*. **24** (1): CD005166. [doi:10.1002/14651858.CD005166.pub2](#). [PMID 17253544](#). **(Retracted, see [doi:10.1002/14651858.cd005166.pub3](#). If this is an intentional citation to a retracted paper, please replace {{Retracted}} with {{Retracted|intentional=yes}}.)**
147. [^](#) Ibáñez L, Ong K, Valls C, Marcos MV, Dunger DB, de Zegher F (August 2006). "Metformin treatment to prevent early puberty in girls with precocious pubarche". *The Journal of Clinical Endocrinology and Metabolism*. **91** (8): 2888–91. [doi:10.1210/jc.2006-0336](#). [PMID 16684823](#).
148. [^](#) Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, Bost F (May 2010). "Metformin in cancer therapy: a new perspective for an old antidiabetic drug?". *Molecular Cancer Therapeutics*. **9** (5): 1092–9. [doi:10.1158/1535-7163.MCT-09-1186](#). [PMID 20442309](#).
149. [^](#) Malek M, Aghili R, Emami Z, Khamseh ME (September 2013). "[Risk of cancer in diabetes: the effect of metformin](#)". *ISRN Endocrinology*. **2013**: 1–9. [doi:10.1155/2013/636927](#). [PMC 3800579](#). [PMID 24224094](#).
150. [^](#) [Jump up to:^a ^b](#) Campbell JM, Bellman SM, Stephenson MD, Lisy K (November 2017). "Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis". *Ageing Research Reviews*. **40**: 31–44. [doi:10.1016/j.arr.2017.08.003](#). [PMID 28802803](#).
151. [^](#) Barzilai, Nir; Crandall, Jill P.; Kritchevsky, Stephen B.; Espeland, Mark A. (June 2016). "[Metformin as a Tool to Target Aging](#)". *Cell Metabolism*. **23** (6): 1060–1065. [doi:10.1016/j.cmet.2016.05.011](#). [PMC 5943638](#). [PMID 27304507](#).

Pioglitazone

From Wikipedia, the free encyclopedia
[Jump to navigation](#)[Jump to search](#)

Pioglitazone	
 	
Gliclazide 30/60 mg (SR) + Metformin 500 mg (SR) + Pioglitazone 15 mg	
Clinical data	
Trade names	Actos, others
AHFS/Drugs.com	Monograph
MedlinePlus	a699016
License data	EU EMA : by INN US FDA : Actos
Pregnancy category	C
Routes of administration	By mouth
Drug class	Thiazolidinedione
ATC code	A10BG03 (WHO)
Legal status	
Legal status	UK: POM (Prescription only) US: R-only
Pharmacokinetic data	

<u>Protein binding</u>	>99%
<u>Metabolism</u>	liver (CYP2C8)
<u>Elimination half-life</u>	3–7 hours
<u>Excretion</u>	in bile
Identifiers	
<u>IUPAC name</u> [show]	
<u>CAS Number</u>	111025-46-8 ✓
<u>PubChem CID</u>	4829
<u>IUPHAR/BPS</u>	2694
<u>DrugBank</u>	DB01132 ✓
<u>ChemSpider</u>	4663 ✓
<u>UNII</u>	X4OV71U42S
<u>KEGG</u>	D08378 ✓
<u>ChEBI</u>	CHEBI:8228 ✓
<u>ChEMBL</u>	ChEMBL595 ✓
<u>CompTox Dashboard</u> (EPA)	DTXSID3037129 
<u>ECHA InfoCard</u>	100.114.441 
Chemical and physical data	
<u>Formula</u>	C ₁₉ H ₂₀ N ₂ O ₃ S
<u>Molar mass</u>	356.44 g/mol g·mol ⁻¹
<u>3D model</u> (JSmol)	Interactive image
<u>Chirality</u>	Racemic mixture
<u>Melting point</u>	183 to 184 °C (361 to 363 °F)
<u>SMILES</u> [show]	
<u>InChI</u> [show]	
(verify)	

Pioglitazone, sold under the brand name **Actos** among others, is a medication used to treat [diabetes mellitus type 2](#).^[1] It may be used with [metformin](#), a [sulfonylurea](#), or [insulin](#).^[1] Use is

recommended together with exercise and diet.^[2] It is not recommended in [diabetes mellitus type 1](#).^[2] It is taken by mouth.^[2]

Common side effects include headaches, muscle pains, inflammation of the throat, and swelling.^[2] Serious side effects may include [bladder cancer](#), [low blood sugar](#), [heart failure](#), and [osteoporosis](#).^{[2][1]} Use is not recommended in [pregnancy](#) or [breastfeeding](#).^[1] It is in the [thiazolidinedione](#) (TZD) class and works by improving sensitivity of tissues to insulin.^[1]

Pioglitazone was patented in 1985 and came into medical use in 1999.^[3] It is available as a [generic medication](#).^[1] A month supply in the United Kingdom costs the [NHS](#) less than £1 as of 2019.^[1] In the United States the wholesale cost of this amount is about 3.20 USD.^[4] In 2016 it was the 116th most prescribed medication in the United States with more than 6 million prescriptions.^[5] It was withdrawn in France and Germany in 2011.^[6]



Contents

Carryl[®] MP 30/60

- 1Medical uses
- 2Contraindications
- 3Side effects
 - 3.1Bladder cancer
- 4Drug interactions
- 5Mechanism of action
- 6Society and culture
 - 6.1Brand names
- 7Research
- 8References
- 9External links

Gliclazide 30/60 mg (SR) + Metformin 500 mg (SR) + Pioglitazone 15 mg

Medical uses^[edit]

Pioglitazone is used to lower blood glucose levels in [diabetes mellitus type 2](#) (T2DM) either alone or in combination with a [sulfonylurea](#), [metformin](#), or [insulin](#).^[2] While pioglitazone does decrease blood sugar levels, the main study that looked at the medication found no difference in the main cardiovascular outcomes that were looked at.^[8] The secondary outcome of death from all causes, myocardial infarction, and stroke were lower.^[8]

Contraindications^[edit]

Pioglitazone cannot be used in patients with a known [hypersensitivity](#) to pioglitazone, other [thiazolidinediones](#) or any of components of its [pharmaceutical](#) forms. It is ineffective and possibly harmful in [diabetes mellitus type 1](#) and [diabetic ketoacidosis](#).^[9] Its safety in pregnancy, [lactation](#) (breastfeeding) and people under 18 is not established.

Given previous experiences with the related drug [troglitazone](#), acute diseases of the liver are regarded as a [contraindication](#) for pioglitazone.

Pioglitazone and all other drugs of its class (thiazolidinediones) are absolutely contraindicated in patients with [heart failure](#).^[9]

Side effects^[edit]

A press release by GlaxoSmithKline in February 2007 noted that there is a greater incidence of fractures of the upper arms, hands and feet in female diabetics given [rosiglitazone](#) compared with those given metformin or glyburide. The information was based on data from the ADOPT trial. Following release of this statement, [Takeda Pharmaceutical Company](#), the developer of pioglitazone (sold as Actos in many markets) admitted that it has similar implications for female patients.^[10]

The risk of [hypoglycemia](#) is low in the absence of other drugs that lower blood glucose.

Pioglitazone can cause [fluid retention](#) and peripheral [edema](#). As a result, it may precipitate [congestive heart failure](#) (which worsens with fluid overload in those at risk). It may cause [anemia](#). Mild weight gain is common due to increase in subcutaneous [adipose tissue](#). In studies, patients on pioglitazone had an increased proportion of upper respiratory tract infection, sinusitis, headache, myalgia and tooth problems.

Chronic administration of the drug has led to occasional instances of [cholestatic hepatitis](#), reversible upon drug discontinuation.^[11]

On July 30, 2007 an Advisory Committee of the Food and Drug Administration concluded that the use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of "myocardial ischemic events" when compared to placebo, but when compared to other diabetes drugs, there was no increased risk. Pioglitazone is currently being reviewed. A [meta-analysis](#) released subsequently showed that pioglitazone reduced the risk of ischemic cardiac events rather than increased the risk, but increased [CHF](#).^[12]

Bladder cancer^[edit]

On June 9, 2011 the [French Agency for the Safety of Health Products](#) decided to withdraw pioglitazone due to high risk of [bladder cancer](#).^[13] This suspension was based on the results of an epidemiological study conducted by the French National Health Insurance. According to the results of the epidemiological study, the French agency found that patients, who were taking Actos for a long time to aid in type 2 diabetes mellitus, significantly increased risk of bladder cancer compared with patients who were taking other diabetes medications.^[14] On June 10, 2011 Germany's [Federal Institute for Drugs and Medical Devices](#) also advised doctors not to prescribe the medication until further investigation of the cancer risk had been conducted.^[15]

On June 15, 2011 the U.S. [FDA](#) announced that pioglitazone use for more than one year may be associated with an increased risk of bladder cancer, and two months later the label was updated with an additional warning about this risk.^[16]

A 2017 meta-analysis of diabetes found no difference in the rates of bladder cancer attributed to the pioglitazone.^[17]

Drug interactions^[edit]



This section **does not cite any sources**. Please help [improve this section](#) by [adding citations to reliable sources](#). Unsourced material may be challenged and [removed](#). (March 2011) ([Learn how and when to remove this template message](#))

Combination with [sulfonylureas](#) or [insulin](#) reciprocally exponentiate risk of [hypoglycemia](#). Therapy with pioglitazone increase the chance of pregnancy in individuals taking oral contraception.

Mechanism of action^[edit]

Pioglitazone selectively stimulates the [nuclear receptor](#) peroxisome proliferator-activated receptor gamma ([PPAR-γ](#)) and to a lesser extent [PPAR-α](#).^{[18][19]} It modulates the transcription of the genes involved in the control of glucose and [lipid metabolism](#) in the [muscle](#), [adipose tissue](#), and the [liver](#).

As a result, pioglitazone reduces [insulin resistance](#) in the liver and peripheral tissues, decreases gluconeogenesis in the liver, and reduces quantity of glucose and [glycated hemoglobin](#) in the bloodstream.

More recently, pioglitazone and other active TZDs have been shown to bind to the [outer mitochondrial membrane](#) protein [mitoNEET](#) with affinity comparable to that of pioglitazone for PPAR γ .^{[20][21]}

Society and culture^[edit]

In 2008 it generated the tenth-highest amount of money for a medication in the U.S. in 2008, with sales exceeding \$2.4 billion.^[22]

Brand names^[edit]

Pioglitazone is marketed as trademarks Actos in the USA, Canada, the UK and Germany, Glustin in Europe, Glizone and Pioz in India by [Zydus Cadila](#) and [USV Limited](#), respectively and Zactos in Mexico by [Takeda Pharmaceuticals](#). On August 17, 2012 the US FDA announced its approval of the first generic version of Actos.^[23]

Research^[edit]

There is tentative research that suggests that pioglitazone may be useful for treating [major depression](#).^[24]

Because it is thought to reduce glial cell activity, it was studied in a small clinical treat in children with [autism](#), under the autoimmune/inflammatory hypotheses of the cause of autism.^[25]

References^[edit]

- [^] ^{Jump up to:^a ^b ^c ^d ^e ^f ^g} *British national formulary : BNF 76 (76 ed.)*. Pharmaceutical Press. 2018. p. 694. ISBN 9780857113382.
- [^] ^{Jump up to:^a ^b ^c ^d ^e} *"Pioglitazone Hydrochloride Monograph for Professionals"*. Drugs.com. American Society of Health-System Pharmacists. Retrieved 3 March 2019.
- [^] Fischer, Jnos; Ganellin, C. Robin (2006). *Analogue-based Drug Discovery*. John Wiley & Sons. p. 450. ISBN 9783527607495.
- [^] *"NADAC as of 2019-02-27"*. Centers for Medicare and Medicaid Services. Retrieved 3 March 2019.
- [^] *"The Top 300 of 2019"*. clincalc.com. Retrieved 22 December 2018.
- [^] Burant, Charles (2012). *Medical Management of Type 2 Diabetes*. American Diabetes Association. p. 63. ISBN 9781580404570.
- [^] *"ACTOS (pioglitazone) Prescribing Information"* (PDF). United States Food and Drug Administration. November 2013.
- [^] ^{Jump up to:^a ^b} Scheen AJ (November 2012). "Outcomes and lessons from the PROactive study". *Diabetes Research and Clinical Practice*. **98** (2): 175–86. doi:10.1016/j.diabres.2012.09.001. PMID 23020930. Since 2005, there has been much debate on the relative value of the statistically non-significant 10% reduction in the quite challenging primary composite endpoint (combining cardiovascular disease-driven and procedural events in all vascular beds) versus the statistically significant 16% decrease in the more robust and conventional main secondary endpoint (all-cause mortality, myocardial infarction, and stroke) observed with pioglitazone.
- [^] ^{Jump up to:^a ^b ^c} U.S. National Library of Medicine (2010). *"ACTOS (pioglitazone hydrochloride) tablet"*. National Institutes of Health. Retrieved 24 December 2012.
- [^] Takeda (March 2007). *"Observation of an Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with ACTOSO (pioglitazone HOI) Tablets for Type 2 Diabetes Mellitus"* (PDF). Retrieved 2012-04-04.
- [^] Baselt R (2008). *Disposition of Toxic Drugs and Chemicals in Man (8th ed.)*. Foster City, CA: Biomedical Publications. pp. 1271–1272.

12. [^](#) [Lincoff AM, Wolski K, Nicholls SJ, Nissen SE \(September 2007\). "Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials". *JAMA*. **298** \(10\): 1180–8. doi:10.1001/jama.298.10.1180. PMID 17848652.](#)
13. [^](#) ["L'antidiabétique Actos retiré du marché" \[Actos antidiabetic withdrawn from the market\]. *Le Figaro* \(in French\). 9 June 2011.](#)
14. [^](#) [Alam II \(1 January 2012\). "France and Germany Suspended Use of Actos for Bladder Cancer Risk". Medical-Reference.](#)
15. [^](#) [Topham, James \(June 10, 2011\). "UPDATE 2-Germany joins France in suspending top Takeda drug". Reuters.](#)
16. [^](#) ["FDA Drug Safety Communication: Updated drug labels for pioglitazone-containing medicines". United States Food and Drug Administration. 4 August 2011.](#)
17. [^](#) [Filipova E, Uzunova K, Kalinov K, Vekov T \(August 2017\). "Pioglitazone and the Risk of Bladder Cancer: A Meta-Analysis". *Diabetes Therapy*. **8** \(4\): 705–726. doi:10.1007/s13300-017-0273-4. PMC 5544610. PMID 28623552.](#)
18. [^](#) [Gillies PS, Dunn CJ \(August 2000\). "Pioglitazone". *Drugs*. **60** \(2\): 333–43, discussion 344–5. doi:10.2165/00003495-200060020-00009. PMID 10983737.](#)
19. [^](#) [Smith U \(September 2001\). "Pioglitazone: mechanism of action". *International Journal of Clinical Practice*. Supplement \(121\): 13–8. PMID 11594239.](#)
20. [^](#) [Colca JR, McDonald WG, Waldon DJ, Leone JW, Lull JM, Bannow CA, Lund ET, Mathews WR \(February 2004\). "Identification of a novel mitochondrial protein \("mitoNEET"\) cross-linked specifically by a thiazolidinedione photoprobe". *American Journal of Physiology. Endocrinology and Metabolism*. **286** \(2\): E252–60. doi:10.1152/ajpendo.00424.2003. PMID 14570702.](#)
21. [^](#) [Paddock ML, Wiley SE, Axelrod HL, Cohen AE, Roy M, Abresch EC, Capraro D, Murphy AN, Nechushtai R, Dixon JE, Jennings PA \(September 2007\). "MitoNEET is a uniquely folded 2Fe 2S outer mitochondrial membrane protein stabilized by pioglitazone". *Proceedings of the National Academy of Sciences of the United States of America*. **104**\(36\): 14342–7. doi:10.1073/pnas.0707189104. PMC 1963346. PMID 17766440.](#)
22. [^](#) ["Details for Actos". Drug Patent Watch.](#)
23. [^](#) ["FDA approves first generic Actos to treat type 2 diabetes". United States Food and Drug Administration. 17 August 2012. Archived from \[the original\]\(#\) on 4 January 2016.](#)
24. [^](#) [Colle R, de Larminat D, Rotenberg S, Hozer F, Hardy P, Verstuyft C, Fève B, Corruble E \(2017\). "Pioglitazone could induce remission in major depression: a meta-analysis". *Neuropsychiatric Disease and Treatment*. **13**: 9–16. doi:10.2147/NDT.S121149. PMC 5182046. PMID 28031713.](#)
25. [^](#) [Doyle CA, McDougale CJ \(August 2012\). "Pharmacotherapy to control behavioral symptoms in children with autism". *Expert Opinion on Pharmacotherapy*. **13** \(11\): 1615–29. doi:10.1517/14656566.2012.674110. PMID 22550944.](#)