Glimepiride

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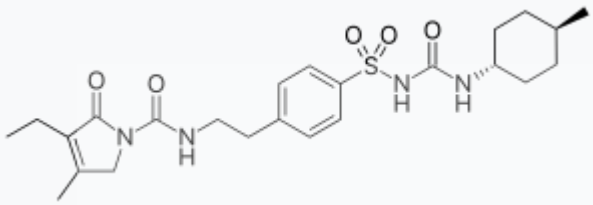
Glimepiride



Clinical data	
Trade names	Amaryl, other
AHFS/Drugs.com	Monograph
MedlinePlus	a696016
License data	EU EMA: by INN
Pregnancy category	US: C (Risk not ruled out)
Routes of administration	By mouth (tablets)
ATC code	A10BB12 (WHO)
Legal status	
Legal status	US: ℞-only In general: ℞ (Prescription only)
Pharmacokinetic data	
Bioavailability	100%
Protein binding	>99.5%
Metabolism	Complete Liver (1st stage through CYP2C9)
Elimination half-life	5–8 hours
Excretion	Urine (~60%), feces (~40%)

Identifiers	
IUPAC name[show]	
CAS Number	93479-97-1✓
PubChem CID	3476
IUPHAR/BPS	6820
DrugBank	DB00222✗
ChemSpider	16740595✓
UNII	6KY687524K
KEGG	D00593✓
ChEBI	CHEBI:5383✗
ChEMBL	ChEMBL1481✓
ECHA InfoCard	100.170.771
Chemical and physical data	
Formula	$C_{24}H_{34}N_4O_5S$
Molar mass	490.617 g/mol g·mol^{-1}
3D model (JSmol)	Interactive image
Melting point	207 °C (405 °F)
SMILES[show]	
InChI[show]	
✗✓ (what is this?) (verify)	

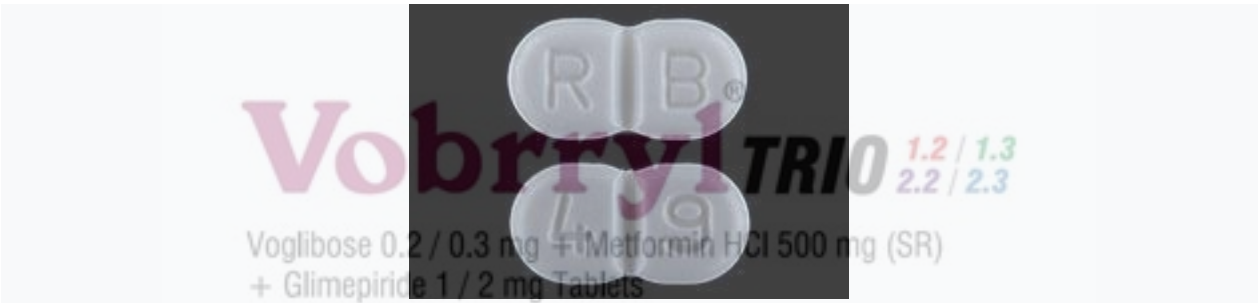
Glimepiride, sold under the trade name **Amaryl** among others, is a medication used to treat diabetes mellitus type 2.[1][2] It is less preferred than metformin.[1] Use is recommended together with diet and exercise.[1] It is taken by mouth.[1] Glimepiride takes up to three hours for maximum effect and lasts for about a day.[1]

Common side effects include headache, nausea, and dizziness.[1] Serious side effects may include low blood sugar.[1] Use in during pregnancy and breastfeeding is not recommended.[3] It works mainly by increasing the amount of insulin released from the pancreas.[1] It is classified as a second-generation sulfonylurea.[4]

Glimepiride was patented in 1979 and approved for medical use in 1995.[5] It is available as a generic medication.[2] A month supply in the United Kingdom costs the NHS about 7.00 £ per month as of 2019.[2] In the United States, the wholesale cost of this amount is about 2.15 USD.[6] In 2016 it was the 61st most prescribed medication in the United States with more than 12 million prescriptions.[7]

Contents

Medical uses[edit]



Two generic oral tablets of glimepiride, 2 mg each

Glimepiride is indicated to treat type 2 diabetes mellitus; its mode of action is to increase insulin secretion by the pancreas. However it requires adequate insulin synthesis as prerequisite to treat appropriately. It is not used for type 1 diabetesbecause in type 1 diabetes the pancreas is not able to produce insulin.[8]

Contraindications[edit]

Its use is contraindicated in patients with hypersensitivity to glimepiride or other sulfonylureas.

Adverse effects[edit]

Side effects from taking glimepiride include gastrointestinal tract (GI) disturbances, occasional allergic reactions, and rarely blood production disorders including thrombocytopenia, leukopenia, and hemolytic anemia. In the initial weeks of treatment, the risk of hypoglycemia may be increased. Alcohol consumption and exposure to sunlight should be restricted because they can worsen side effects.[8]

Interactions[edit]

Nonsteroidal anti-inflammatory drugs (such as salicylates), sulfonamides, chloramphenicol, coumadin and probenecid may potentiate the hypoglycemic action of glimepiride. Thiazides, other diuretics, phothiazides, thyroid products, oral contraceptives, and phenytoin tend to produce hyperglycemia.

Mechanism of action[edit]

Like all sulfonylureas, glimepiride acts as an insulin secretagogue.[9] It lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors.

Not all secondary sufonylureas have the same risk of hypoglycemia. Glibenclamide (glyburide) is associated with an incidence of hypoglycemia of up to 20–30%, compared to as low as 2% to 4% with glimepiride. Glibenclamide also interferes with the normal homeostatic suppression of insulin secretion in reaction to hypoglycemia, whereas glimepiride does not. Also, glibenclamide diminishes glucagon secretion in reaction to hypoglycemia, whereas glimepiride does not.[10]

Pharmacokinetics[edit]

Gastrointestinal absorption is complete, with no interference from meals. Significant absorption can occur within one hour, and distribution is throughout the body, 99.5% bound to plasma protein. Metabolism is by oxidative biotransformation, it is hepatic and complete. First, the medication is metabolized to M_1 metabolite by CYP2C9. M_1 possesses about ⅓of pharmacological activity of glimepiride, yet it is unknown if this results in clinically meaningful effect on blood glucose. M_1 is further metabolized to M_2 metabolite by cytosolic enzymes. M_2 is pharmacologically inactive. Excretion in the urine is about 65%, and the remainder is excreted in the feces.

References[edit]

1. ^ Jump up to:[a] [b] [c] [d] [e] [f] [g] [h] *"Glimepiride Monograph for Professionals". Drugs.com. American Society of Health-System Pharmacists. Retrieved 3 March 2019.*
2. ^ Jump up to:[a] [b] [c] *British national formulary : BNF 76 (76 ed.). Pharmaceutical Press. 2018. p. 693. ISBN 9780857113382.*
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6. ^ *"NADAC as of 2019-02-27". Centers for Medicare and Medicaid Services. Retrieved 3 March 2019.*
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10. ^ *Davis, Stephen N. (2005). "60. Insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas". In Brunton, Laurence L.; Lazo, John S.; Parker, Keith L. (eds.) (eds.). Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill. p. 1636. ISBN 0-07-142280-3.*

Metformin

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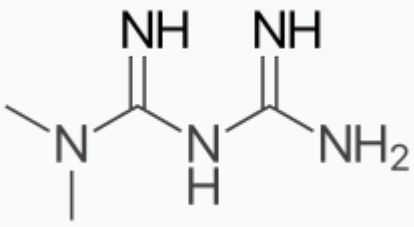
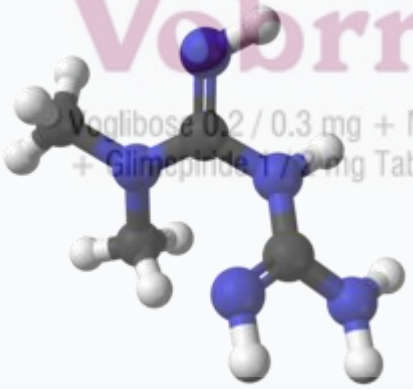
Metformin





Clinical data	
Pronunciation	/mɛtˈfɔːrmɪn/, *met-FOR-min*
Trade names	Glucophage, other
Synonyms	*N*,*N*-dimethylbiguanide[1]
AHFS/Drugs.com	Monograph
MedlinePlus	a696005
License data	EU EMA: by INN US FDA: metformin
Pregnancy	AU: C

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

Chemical and physical data	
Formula	$C_4H_{11}N_5$
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 worldwas 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

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.[50][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]

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 B_{12}.[62][63] Higher doses and prolonged use are associated with increased incidence of vitamin B_{12} 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 m^2.[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 H_2-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 cephalexin 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]

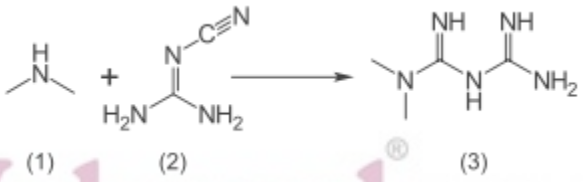
Activation of AMPK was required for metformin's inhibitory effect on liver glucose production.[89] AMPK is an enzyme that plays an important role in insulin signalling, whole body energy balance and the metabolism of glucose and fats.[90] AMPK Activation was required for an increase in the expression 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 GLUT4enhancer 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.[110][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 Tevareceived 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**

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Voglibose

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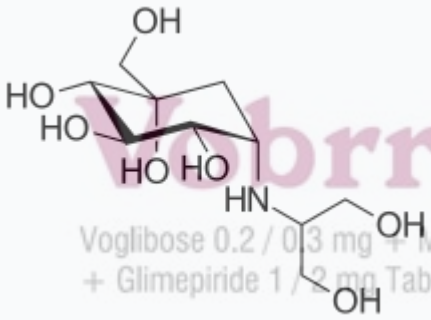
Voglibose



Clinical data	
AHFS/Drugs.com	International Drug Names
ATC code	A10BF03 (WHO)
Identifiers	
IUPAC name[show]	
CAS Number	83480-29-9✓
PubChem CID	444020
DrugBank	DB04878✓
ChemSpider	392046✓
UNII	S77P977AG8
KEGG	D01665✓
ChEMBL	ChEMBL476960✓
CompTox Dashboard(EPA)	DTXSID2021442

Chemical and physical data	
Formula	$C_{10}H_{21}NO_7$
Molar mass	267.28 g/mol g·mol^{-1}
3D model (JSmol)	Interactive image
SMILES[show]	
InChI[show]	
(verify)	

Voglibose (INN and USAN, trade name **Voglib**, marketed by Mascot Health Series) is an alpha-glucosidase inhibitor used for lowering post-prandial blood glucose levels in people with diabetes mellitus. Voglibose delays the absorption of glucose thereby reducing the risk of macrovascular complications. Voglibose is a research product of Takeda Pharmaceutical Company, Japan's largest pharmaceutical company. Voglibose was first launched in 1994, under the trade name BASEN, to improve postprandial hyperglycemia in diabetes mellitus.[1]

Postprandial hyperglycemia (PPHG) is primarily due to first phase insulin secretion. Alpha glucosidase inhibitors delay glucose absorption at the intestine level and thereby prevent sudden surge of glucose after a meal.

There are three drugs which belong to this class, acarbose, miglitol and voglibose, of which voglibose is the newest.

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