METFORMIN (Systemic)

Category

Antihyperglycemic agent 1, 2.

Indications

Accepted

Type 2 diabetes (treatment)¾Metformin is indicated in patients with type 2 diabetes to control hyperglycemia that cannot be controlled by diet management, exercise, or weight reduction, or when insulin therapy is not required or feasible. 1, 2, 3, 8 It is used as monotherapy or as an adjunct to sulfonylureas or insulin * when either alone does not achieve adequate glycemic control. 1 It can be tried if primary or secondary failure of sulfonylureas occurs. However, caution and clinical judgment should be used when combining metformin with maximum doses of sulfonylureas for treating nonobese patients with type 2 diabetes who clearly are not responding to the sulfonylureas; insulin may be the preferred treatment in such cases. 4

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Metformin potentiates the effect of insulin by mechanisms not fully understood. 2, 3, 8 Metformin does not stimulate pancreatic beta cells to increase secretion of insulin; insulin secretion must be present for metformin to work properly. 2, 3, 8 It is postulated that metformin decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. 1

Specifically, it is thought that metformin may increase the number and/or affinity of insulin receptors on cell surface membranes, especially at peripheral receptor sites, and help to correct down regulation of the insulin receptor. This effect increases the sensitivity to insulin at receptor and postreceptor binding sites and increases glucose uptake peripherally. 5 Insulin concentrations remain unchanged or are slightly reduced as glucose metabolism improves. 1 At therapeutic doses, metformin does not cause hypoglycemia in diabetic or nondiabetic individuals. 2, 3 In addition, metformin's metabolic effects increase hepatic glycogen stores in diabetic patients (but not in nondiabetic patients), reduce fatty acid oxidation and acetyl coenzyme A formation, and may decrease intestinal glucose absorption. Glucose uptake and free fatty acid oxidation are effects considered to be caused by non-insulin-mediated mechanisms. Some studies have shown lipid-lowering effects in both diabetic and nondiabetic patients, while others have shown no clear evidence that metformin decreases lipid concentrations in all diabetic patients. These effects could manifest as weight reduction with nominal disturbance of the metabolic rate. 4, 6

Other actions/effects:

Metformin interferes with the absorption of vitamin B 12 by competitive inhibition of calcium-dependent binding of the intrinsic factor-vitamin B 12 complex to its receptor; anemia in predisposed individuals is possible. 1

Precautions to Consider

Carcinogenicity

A study in rats and in mice for 104 weeks and 91 weeks, respectively, at three times the recommended human daily dose showed no evidence of carcinogenicity. 1

Tumorigenicity

A study in male rats showed no evidence of tumorigenicity; however, female rats given three times the recommended human daily dose on a mg per kg of body weight (mg/kg) basis, or 900 mg a day, had an increased incidence of benign stromal uterine polyps. 1

Mutagenicity

Metformin was not found to be mutagenic in the Ames test, gene mutation test (mouse lymphoma cells), chromosome aberration test (human lymphocytes), or in vivo micronuclei formation test (mouse bone marrow). 1

Pregnancy/Reproduction

Fertility¾Problems in humans have not been documented.
No evidence of impairment of fertility was found in male or female rats given twice the recommended human daily dose of metformin. 1

Pregnancy¾Adequate and well-controlled studies in humans have not been done. 1 Control of blood glucose during pregnancy with diet alone or a combination of diet and insulin is recommended, while use of all oral antidiabetic agents is discouraged. Use of insulin rather than metformin for the treatment of type 2 diabetes and gestational diabetes mellitus (GDM) permits maintenance of blood glucose at concentrations as close to normal as possible. 14, 50 High blood glucose concentrations have been associated with a higher incidence of major congenital abnormalities early in pregnancy (5 to 8 weeks gestation) and high perinatal morbidity and mortality later in pregnancy. 48, 49, 50 A study reported infant malformation rates of 35, 12.9, and 4.8% when initial hemoglobin A 1c (an indicator of blood glucose control for the preceding 3 months) was 10% or more, 8 to 9.9%, and below 8%, respectively. The malformation rate in infants born to mothers who do not have diabetes is approximately 2%. 51, 52

Teratological studies in albino rats found no abnormalities.
FDA Pregnancy Category B. 1

Breast-feeding

Problems in humans have not been documented. Metformin is distributed into breast milk. 1

Pediatrics

No information is available on the relationship of age to the effects of metformin in pediatric patients. Safety and efficacy have not been established. 1

Adolescents

No information is available on the relationship of age to the effects of metformin in adolescent patients. Safety and efficacy have not been established. 44

Geriatrics

Appropriate studies performed to date have not demonstrated geriatrics-specific problems that would limit the usefulness of metformin in the elderly. 16 However, because of possible gastrointestinal intolerance, it is recommended that treatment be initiated with low doses that are adjusted gradually, according to renal clearance. Maximum doses should not be used. Elderly patients are more likely to have age-related renal function impairment or peripheral vascular disease, which may require adjustment of dosage or dosage interval, or discontinuation of treatment when appropriate. 1, 15, 16

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Administration of any medication that may affect metabolic or glycemic control of diabetes mellitus requires careful monitoring of blood glucose concentrations by the patient or health care professional. This is particularly important when any medication is added to or removed from an established treatment regimen. Subsequent adjustments in diet or in dose of antidiabetic agent or both may be necessary; these adjustments may differ depending on the severity of the diabetes.
>> Alcohol, acute or chronic ingestion of 1, 2, 3, 8

(excessive intake may elevate blood lactate concentrations or increase the risk of developing hypoglycemia, especially when alcohol is ingested without meals 2, 8)

>> Cimetidine 1 or

>> Other cationic medications excreted by renal tubular transport, such as:
Amiloride 1

Calcium channel blocking agents, especially nifedipine 1

Digoxin 1

Morphine 1

Procainamide 1

Quinidine 1

Quinine 1

Ranitidine 1

Triamterene 1

Trimethoprim 1

Vancomycin 1

(cimetidine inhibits the renal tubular secretion of metformin, decreases renal clearance of metformin by 27% over 24 hours, and can significantly increase plasma concentrations of metformin by 60% for up to 6 hours when cimetidine and metformin are taken together; clinical significance is not known, but dosage reduction of metformin potentially may be needed 1, 17)
(nifedipine increased absorption of metformin in a single-dose study, resulting in a 9% increase in area under the concentration-time curve [AUC] and a 20% increase in peak plasma concentration with no change in half-life and urinary excretion; clinical significance is not known; it is not known whether similar effects are produced by other calcium channel blocking agents 1)
(other cationic medications excreted by renal tubular transport have the potential to increase metformin's plasma concentration or interfere with renal clearance; careful monitoring of blood glucose would be especially appropriate when these medications are given concurrently with metformin 1)

>> Furosemide 1, 2, 3

(in one study, furosemide increased metformin's AUC by 15% in normal healthy volunteers; renal clearance was not affected; clinical significance is not known, but dosage reduction of metformin potentially may be needed 1)

Hyperglycemia-causing medications, such as:
Contraceptives, estrogen-containing, oral 1, 2, 3, 8

Corticosteroids 1, 2, 3, 8

Diuretics, thiazide 1, 2, 3, 8

Estrogens 1

Isoniazid 1

Niacin 1, 2, 3, 8

Phenothiazines, 1 especially chlorpromazine
Phenytoin 1

Sympathomimetic agents 1

Thyroid hormones 1

(these medications may contribute to hyperglycemia; an increased dose of metformin or a change to another antidiabetic agent may be needed 1, 55)

Hypoglycemia-causing medications, such as:
Clofibrate 2, 3, 8

Monoamine oxidase (MAO) inhibitors 2, 3, 8

Probenecid 2, 3, 8

Propranolol 2, 3, 8

Rifabutin 8

Rifampin 2, 3, 8

Salicylates 2, 3, 8

Sulfonamides, long-acting 2, 3, 8

Sulfonylureas 2, 3

(these medications may cause hypoglycemia and decrease the dosage of metformin needed; although studies with many of these agents in combination with metformin have not been done, it is expected that those medications that are highly protein-bound will cause fewer problems when used with metformin than when used with some of the sulfonylurea antidiabetic agents 1, 55)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Ketones, urine

(may produce false-positive tests 18)

With physiology/laboratory test values

Cholesterol, total, serum or

Lipoproteins, low-density (LDL), serum or

Triglycerides, serum

(the effects of metformin on these lipid subfractions in patients with type 2 diabetes are inconsistent and may depend on weight control; further studies are needed to fully characterize these effects. Generally, concentrations of cholesterol, low-density lipoproteins, or triglycerides may be lowered or unchanged in metformin users. This is thought to be independent of metformin's glucose-lowering effect; it may involve suppression of free fatty acid oxidation and lipid oxidation or reduction in the triglyceride content of the LDL and very low-density lipoprotein [VLDL] fractions by metformin 19, 20, 21, 22, 23, 24, 25)

Lactate, fasting, serum 10, 48

(may increase to the upper range of normal, 2 mEq/L [2 mmol/L], or show no change with therapeutic doses; although the source is unknown, any small increase is thought to be due to glucose metabolism in the splanchnic beds, not in skeletal muscle 10)

Lipoproteins, high-density (HDL), serum

(may be slightly increased or unchanged 19, 20, 21, 22, 23, 24, 25)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Any condition needing close blood glucose control, such as:
Burns, severe
Dehydration 1, 2, 3, 8

Diabetic coma 1, 2, 3, 8

Diabetic ketoacidosis 1, 2, 3, 8

Hyperosmolar nonketotic coma 1, 2, 3, 8

Infection, severe 2, 3, 8, 33

Surgery, major 1, 2, 3, 8

Trauma, severe 2, 3, 8

(risks of side effects related to uncontrolled blood glucose or lactic acidosis may be increased, and metformin should be discontinued; insulin controls blood glucose best in patients with these conditions; also, metformin should be discontinued 2 days prior to surgery 1, 2, 3, 4, 33)

>> Conditions associated with hypoxemia, 1, 2, 3, 8 such as:

Cardiorespiratory insufficiency 2, 3, 8, 10

Cardiovascular collapse 1, 2, 3, 8, 10

Congestive heart failure 1, 2, 3, 10

Myocardial infarction, acute 1, 2, 3, 10 or

>> Hepatic disease, severe, acute, or chronic 1, 2, 3, 8, 10, 33 or

>> Lactic acidosis, active or history of 2, 3, 8, 10 or

>> Renal function impairment or renal disease 1, 2, 3, 8, 10, 33

(lactic acidosis is associated with these conditions and the risk is further increased when metformin is given concurrently 1, 2, 3, 10)
(risk of lactic acidosis increases with the degree of renal dysfunction, impairment of renal clearance, and age of patient; patients who have demonstrated fasting serum lactate values above the upper limit of normal should not receive metformin 1, 2, 3, 10)

>> Diagnostic or medical examinations using intravascular iodinated contrast media such as:
Angiography 1, 2, 3, 8

Cholangiography, intravenous 1

Computed tomography (CT) scan 1

Pyelography 2, 3, 8

Urography 1

(because of the increased risk of lactic acidosis, metformin should be discontinued at the time of or prior to medical or diagnostic examinations requiring use of contrast media that can cause functional oliguria; metformin therapy should be withheld for 48 hours after the procedure and should not be reinstated until after renal function returns to normal 1)

>> Hypersensitivity to metformin 1, 8

Risk-benefit should be considered when the following medical problems exist

>> Diarrhea or

>> Gastroparesis or

>> Intestinal obstruction or

>> Vomiting or

>> Other conditions causing delayed food absorption 53

(conditions that decrease or delay stomach emptying may require a modification of metformin dose or a change to insulin 55)

>> Hyperglycemia-causing conditions, such as:
Female hormonal changes
Fever, high 1

Hypercortisolism, not optimally treated
Psychological stress 1, 2, 3

(these conditions, by increasing blood glucose, may increase the need for more frequent glucose monitoring and increase the need for a temporary or permanent dose increase of metformin or a change to insulin if blood glucose is uncontrolled 1, 55)

>> Hyperthyroidism, not optimally controlled

(hyperthyroidism aggravates diabetes mellitus by increasing plasma glucose concentrations and glucose absorption and impairing glucose tolerance; thyroid hormone has dose-dependent biphasic effects on glycogenolysis and gluconeogenesis, which can make glycemic control difficult until the patient is euthyroid; patients with hyperthyroidism may require an increased dose of metformin until euthyroidism is achieved 55)

>> Hypoglycemia-causing conditions, such as:
Adrenal insufficiency, not optimally controlled 1

Debilitated physical condition 1

Malnutrition 1

Pituitary insufficiency, not optimally controlled 1

(these conditions, which inherently predispose patients to the risk of developing hypoglycemia, increase the patient's risk of developing severe hypoglycemia during metformin treatment; reduction of metformin dose or more frequent blood glucose monitoring may be required 55)

>> Hypothyroidism, not optimally controlled

(this condition is associated with reduced glucose absorption and altered glucose and lipoprotein metabolism; lower-than-normal doses of metformin may be needed when hypothyroid conditions exist, although an increase in metformin dose may be required when initiating thyroid treatment; glucose control may be difficult until the patient is euthyroid 55)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

Folic acid concentrations, serum 2, 3, 10 and

Vitamin B 12 concentrations, serum 1, 2, 3, 8, 10

(recommended every 1 or 2 years during long-term metformin therapy because metformin may interfere with their absorption 1, 2, 3, 8)

>> Glucose concentration, blood or serum 1, 2, 3

(blood or serum glucose reflects the current degree of metabolic control and should be routinely self-monitored by the patient at home and by the physician [every 3 months, or more often when patient is not stabilized] to confirm that blood glucose concentration is maintained within agreed-upon targets by the selected diet and dosing regimen; this is particularly important during dosage adjustments. Self-monitoring of blood glucose by the patient may require testing several times a day or once to several times a week 26, 27, 28, 29, 30, 31)
(caution in interpreting blood glucose concentrations is needed because normal whole blood glucose values are approximately 15% lower than serum glucose values; glucose values are also laboratory- and method-specific. Normal fasting whole blood glucose for adults of all ages is 65 to 95 mg/dL [3.6 to 5.3 mmol/L]. Normal fasting serum glucose is 70 to 105 mg/dL [3.9 to 5.8 mmol/L] for adults younger than 60 years of age and 80 to 115 mg/dL [4.4 to 6.4 mmol/L] for adults 60 years of age or older. For pregnant women with diabetes, a normal fasting serum glucose is less than 105 mg/dL [5.8 mmol/L] and a fasting whole blood glucose is less than 120 mg/dL [6.7 mmol/L] 2, 3, 26, 27, 28, 29, 30, 31)
(capillary blood glucose measurement provides important information when done properly, but caution is warranted because of potential errors in technique and readings; it has been suggested that the values be relied upon only if the reported glucose concentration for patients whose diabetes is stable is between 75 mg/dL and 325 mg/dL [4.16 mmol/L and 17.88 mmol/L, respectively] 26, 27, 28, 29, 30, 31)

Glucose concentrations, urine and

Ketone concentrations, urine 1

(if blood glucose concentrations exceed 200 mg/dL [11.1 mmol/L], monitoring of urine for the presence of glucose and ketones may be necessary; normalization of glucose in the urine generally lags quantitatively behind serum glucose concentrations; test methods are generally capable of detecting glucose concentrations in the urine greater than 180 mg/dL [10 mmol/L] 2, 3)

>> Glycosylated hemoglobin (hemoglobin A 1c) determinations 1, 26, 27, 28, 29, 30, 31

(monitoring should be done every 3 months or as often as necessary; assessment of this parameter does not eliminate the need for daily blood glucose monitoring. Hemoglobin A 1c values reflect the blood glucose control over the preceding 3 months. Normal whole blood hemoglobin A 1c is approximately 4 to 6% of total hemoglobin; specific values are laboratory-dependent. Hemoglobin A 1c is falsely elevated in patients whose diabetes is unstable when the intermediate precursor is elevated [e.g., in alcoholism] and falsely lowered in conditions of shortened red blood cell life span [e.g., in anemia and acute or chronic blood loss] or in patients with hemoglobinopathies [e.g., sickle cell disease] 1)

Hematocrit 1 and

Hemoglobin concentrations 1 and

Red blood cell indices 1

(recommended upon initiation of metformin therapy and annually thereafter 1)

Physical examinations

(regular examinations as often as necessary to reassess appropriateness of continuation of metformin therapy)

>> Renal function assessment 1, 2, 3, 10

(recommended annually or more often for patients in whom the risk of developing lactic acidosis is increased)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Anemia, megaloblastic (tiredness; weakness) 1, 10, 34; hypoglycemia (anxiety; behavior change similar to drunkenness; blurred vision; cold sweats; confusion; cool, pale skin; difficulty in concentrating; drowsiness; excessive hunger; fast heartbeat; headache; nausea; nervousness; nightmares; restless sleep; shakiness; slurred speech; unusual tiredness or weakness); lactic acidosis (diarrhea; fast, shallow breathing; muscle pain or cramping; unusual sleepiness; unusual tiredness or weakness) 1, 10, 32, 33, 34

Note: Hypoglycemia does not usually occur with use of metformin unless predisposing conditions or factors are present, such as unusual fasting, concurrent use of other antidiabetic agents, or toxic doses of metformin. Metformin, in combination with sulfonylureas, has been reported to lower basal glucose concentrations typically by at least 20% more than do sulfonylureas used alone. 1, 10, 33, 35, 37, 48

Lactic acidosis is a potentially fatal complication. The cases reported have occurred primarily in patients in whom a contraindication existed; 1, 2, 3 otherwise, the risk is minimal with use of metformin. Patients usually presented not with symptoms of lactic acidosis, but rather with acute symptoms of other problems that resulted in metformin accumulation because of renal function impairment or failure in conditions such as myocardial infarction or renal or hepatic disease. 4, 7, 10, 44, 54

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Anorexia (loss of appetite) 1, 2, 3, 8; diarrhea 1, 2, 3; dyspepsia (stomachache) 2, 3; flatulence (passing of gas) 1; headache; metallic taste 2, 3, 8; nausea 1, 2, 3, 8; vomiting 1, 2, 3, 8; weight loss 1, 35, 36, 37, 38

Note: Diarrhea, dyspepsia, and nausea occur less frequently when small doses are used initially and, along with headache and metallic taste, are transient. If diarrhea occurs after several months of metformin therapy, lactic acidosis should be considered. 4, 10, 35, 36, 37, 38

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Hypoglycemia; lactic acidosis 1

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Metformin (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Hypersensitivity to metformin
Pregnancy¾Use of any oral antidiabetic medication is discouraged during pregnancy; diet or diet/insulin is recommended to prevent maternal and fetal problems; importance of controlling and monitoring blood glucose during pregnancy; alerting physician if planning to become pregnant
Breast-feeding¾Metformin is distributed into breast milk
Use in the elderly¾Age-related renal function impairment or peripheral vascular disease may require discontinuation of metformin treatment or special precautions in the elderly
Other medications, especially alcohol, amiloride, calcium channel blocking agents, cimetidine, digoxin, furosemide, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin, or any other cationic medication excreted by renal transport
Other medical problems, especially hepatic disease (severe, acute, or chronic); hyperthyroidism or hypothyroidism (not optimally controlled); lactic acidosis (active or history of); renal function impairment or renal disease; conditions associated with hypoxemia; conditions causing delayed food absorption (e.g., diarrhea, gastroparesis, intestinal obstruction, or vomiting); conditions causing hyperglycemia or hypoglycemia; or conditions needing close blood glucose control
Proper use of this medication

>> Compliance with therapy, including not taking more or less medication than directed

>> Alternative dosing or therapy changes for modifications in blood glucose testing, diet, exercise, fluid replacement, and sick-day management

>> Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Regular visits to physician to check progress

>> Carefully following special instructions of health care team:
Discussing use of alcohol
Not taking other medications unless discussed with physician
Getting counseling for family members to help them assist the patient with diabetes; also, special counseling for pregnancy planning and contraception
Travel considerations

>> Preparing for and understanding what to do in case of an emergency; having or wearing medical identification and keeping a glucagon kit and quick-acting source of sugar close by

>> Informing physician of metformin therapy when medical examinations that require administration of contrast media are scheduled or when surgery is scheduled; metformin should be discontinued before surgery or appropriate medical tests and may be reinstated 48 hours postprocedure if renal function is normal

>> Recognizing symptoms of lactic acidosis, such as diarrhea, fast and shallow breathing, severe muscle pain or cramping, unusual sleepiness, and unusual tiredness and weakness

>> Knowing what to do if symptoms of lactic acidosis occur, such as checking blood glucose and getting immediate emergency medical help; checking with physician if vomiting occurs

>> Recognizing symptoms of hypoglycemia, such as anxiety; behavior change similar to drunkenness; blurred vision; cold sweats; confusion; cool, pale skin; difficulty in concentrating; drowsiness; excessive hunger; fast heartbeat; headache; nausea; nervousness; nightmares; restless sleep; shakiness; slurred speech; and unusual tiredness and weakness

>> Recognizing what brings on symptoms of hypoglycemia, such as delaying or missing a meal or snack, exercising more than usual, drinking significant amounts of alcohol, taking certain medications, using too much antidiabetic medication (insulin or a sulfonylurea), or illness, especially with vomiting or diarrhea

>> Knowing what to do if symptoms of hypoglycemia occur, such as using glucagon in emergency situations including when unconsciousness occurs; eating glucose tablets or gel, sugar cubes, corn syrup, or honey; or drinking fruit juice, nondiet soft drink, or sugar dissolved in water; not eating foods high in fat, such as chocolate, since fat slows gastric emptying; also, eating a small snack, such as crackers or half sandwich, when scheduled meal is longer than 1 hour away

>> Recognizing symptoms of hyperglycemia and ketoacidosis, such as blurred vision; drowsiness; dry mouth; flushed, dry skin; fruit-like breath odor; increased frequency and volume of urination; ketones in urine; loss of appetite; nausea or vomiting; stomachache; tiredness; troubled breathing (rapid and deep); unconsciousness; and unusual thirst

>> Recognizing what brings on symptoms of hyperglycemia, such as fever or infection; not taking enough or missing a dose of antidiabetic medication; exercising less than usual; taking certain medications; or overeating or not following meal plan

>> Knowing what to do if symptoms of hyperglycemia occur, such as checking blood glucose and contacting a member of the health care team

Side/adverse effects

Signs and symptoms of potential side effects, especially megaloblastic anemia, hypoglycemia, and lactic acidosis

General Dosing Information

Individual determination of the minimum dose of metformin that lowers blood glucose adequately is recommended. Short-term treatment during periods of transient loss of glucose control may be sufficient for some patients. Some clinicians recommend that metformin be discontinued annually or semi-annually to assess its continued contribution to the control of blood glucose concentrations, especially if there are progressive signs of secondary failure. Metformin should be discontinued if it is not significantly contributing to disease management. 1, 2, 3, 8

Metformin should be withdrawn or the dose reduced temporarily if vomiting occurs. Treatment may be resumed cautiously after the possibility of lactic acidosis has been excluded. 2, 3, 10

When transferring a patient from a sulfonylurea to metformin, no transition period is necessary, except when chlorpropamide has been used for treatment. Chlorpropamide's prolonged action requires more frequent monitoring for hypoglycemia during the first 2 weeks following the transition. 1, 10

When adding a sulfonylurea to maximum doses of metformin or metformin to maximum doses of a sulfonylurea, even if primary or secondary failure of a sulfonylurea has occurred, the new medication should be added gradually and titrated to the lowest effective dose. 1, 45, 46, 48 Both agents should be discontinued and insulin should be initiated if the patient does not respond to maximum doses within 3 months (or less, depending on clinician's decision). 1

Diet/Nutrition

Metformin should be taken with food to reduce gastrointestinal symptoms. 1, 2, 3

For treatment of adverse effects and/or overdose

Recommended treatment consists of the following: For treatment of lactic acidosis

· Hemodialysis with sodium bicarbonate has been used but is controversial because published information concerning outcome is lacking and few cases of metformin-induced lactic acidosis have

been reported; peritoneal dialysis also has been used, but hemodialysis is thought to be the preferred method when dialysis is needed, such as in patients with shock syndrome. Because of metformin's rapid renal elimination, dialysis is probably not necessary when renal function can be restored. 13, 32, 43 Dialysis solutions containing lactate as the buffering agent should not be used in cases of metformin-induced lactic acidosis. 32 For mild to moderate hypoglycemia

· Treating with immediate ingestion of a source of glucose, such as glucose gel, glucose tablets, fruit juice, corn syrup, nondiet soft drinks, honey, sugar cubes, or table sugar dissolved in water. A frequently used source of glucose is a glassful of orange juice containing 2 or 3 teaspoonfuls of table sugar. 39

· Documenting blood glucose and rechecking in 15 minutes.
· Counseling patient to seek medical assistance promptly.
· Possible adjustment of metformin dosage.
· Possible adjustment of meal pattern. 39, 40, 41, 42 For severe hypoglycemia or acute overdose, including coma

Note: Dextrose administration is the basis for treatment of hypoglycemia; however, an exposure to sudden hyperglycemia caused by a rapid injection of hypertonic dextrose injection may further stimulate the sulfonylurea-primed pancreas when sulfonylureas are used with metformin to release more insulin, worsening the hypoglycemia. 39, 42

· Counseling patient to obtain emergency medical assistance immediately.
· Immediately treating with 50 mL of 50% dextrose injection given intravenously to stabilize the patient. Then, administering a continuous infusion of 5 to 10% dextrose injection to maintain slight hyperglycemia (approximately 100 mg/dL [5.55 mmol/L] blood glucose concentration) for up to 12 days. Intravenous dextrose therapy should not be terminated suddenly. Oral dextrose cannot be relied upon to maintain euglycemia because 60% of an oral dextrose dose is stored as hepatic glycogen with only 15% left for brain utilization and 15% for insulin-dependent tissues. 40, 42

· Glucagon, 1 to 2 mg administered intramuscularly, is useful for fast onset of action to mobilize hepatic glucose stores but may be ineffective or variable in its effect if glycogen stores are depleted. Therefore, glucagon should be administered after dextrose administration. 40

· Diazoxide (200 mg orally every 4 hours or 300 mg intravenously over a 30-minute period every 4 hours) can be used for patients who do not respond to dextrose therapy or for patients in a coma as an aid to dextrose infusion to reduce hypoglycemia; the patient must be monitored for sodium concentration and hypotension. 40, 42

· Emesis can be induced with ipecac syrup if the metformin overdose is recent (within the past 30 minutes) and if the patient is alert, has an intact gag reflex, and is not obtunded or convulsing. Otherwise, gastric lavage is required after endotracheal tube placement. 40, 42

· Gastric decontamination by administration of repeated doses of oral activated charcoal with the appropriate cathartic may be attempted, although the usefulness of this regimen has not been established. 40

· Monitoring vital signs, arterial blood gases, blood glucose, and serum electrolytes (especially calcium, potassium, and sodium) as required. Initially, blood glucose concentrations should be monitored as

frequently as every 1 to 3 hours. Blood urea nitrogen and serum creatinine concentrations should also be obtained. 40

· Cerebral edema¾Managing with mannitol and dexamethasone. 40

· Hypokalemia¾Managing with potassium supplements. 40

· Hospitalization for 6 to 91 hours (mean, 24 hours), because the hypoglycemia may be recurrent and prolonged. 39, 40, 41, 42

· Other supportive measures should also be employed as needed.

Oral Dosage Forms

METFORMIN HYDROCHLORIDE TABLETS

Usual adult dose

Antihyperglycemic agent¾
As monotherapy¾
Initial¾Oral, 500 mg two times a day, taken with morning and evening meals. The daily dose may be increased by 500 mg at weekly intervals as needed. 1 An alternative dose is 850 mg a day, taken with the morning meal. The daily dose may be increased by 850 mg at fourteen-day intervals. 1

Maintenance¾Oral, 500 or 850 mg two to three times a day, taken with meals. 1

In combination with a sulfonylurea¾
The dosage of each agent must be adjusted until the desired degree of glycemic control is achieved. 1

In combination with insulin *¾
Oral, initially 500 mg a day. The dosage may be increased by 500 mg at weekly intervals as needed. 1

Note:
The current insulin dose should be continued upon initiation of metformin therapy. However, the insulin dose should be decreased by 10 to 25% when the fasting plasma glucose concentration decreases to less than 120 mg per dL (6.7 mmol per L). 1

Usual adult prescribing limits

2550 mg a day. 1, 2

Usual pediatric dose

Safety and efficacy have not been established. 1

Usual geriatric dose

See Usual adult dose. For some sensitive individuals, lower initial doses may be needed. Maximum doses are not advised for use in the elderly. 1

Strength(s) usually available

U.S.¾500 mg (Rx)[Glucophage (scored) 1]

850 mg (Rx)[Glucophage (scored) 1]

Canada¾500 mg (Rx)[Apo-Metformin (scored) 47] [Gen-Metformin 56] [Glucophage (scored) 2] [Glycon 8] [Novo-Metformin (scored) 3] [Nu-Metformin (scored) 12]

850 mg (Rx)[Apo-Metformin 47] [Glucophage 2] [Novo-Metformin 3] [Nu-Metformin 12]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) 1, 8, 47, 56 in a light-resistant container, 1, 8 unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food. 2, 3

· Do not drink alcohol.

References

1 Glucophage package insert (Bristol-Myers Squibb¾US), Rev 11/98, Rec 11/12/98.

2 Glucophage (Hoechst Marion Roussel). In: Gillis MC, editor. CPS Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa: Canadian Pharmacists Association; 1998. p. 673.

3 Novo-Metformin product monograph (Novopharm¾Canada), Rev 7/93, Rec 8/94.

4 Watkins PJ. Guidelines for good practice in the diagnosis and treatment of non-insulin-dependent diabetes mellitus. Report of a joint working party of the British Diabetic Association, the Research Unit of the Royal College of Physicians, and the Royal College of General Practitioners. J R Coll Physicians Lond 1993 Jul; 27(3): 259-66.

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