



Texas Medicaid/CHIP Vendor Drug Program

Drug Utilization Criteria For Outpatient Use Guidelines

Oral Antidiabetic Agents

About

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

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1. Dosage [*]

Oral antidiabetic agents are FDA-approved for use in type 2 diabetics as monotherapy or in combination with other oral antidiabetic agents or insulin, when the single agent alone, in addition to diet and exercise, does not provide sufficient glycemic control.

Oral sulfonylureas reduce blood glucose by stimulating insulin from pancreatic beta-cells as well as increasing responsiveness in insulin-sensitive tissues. Although structurally dissimilar from oral sulfonylureas, meglitinides also stimulate insulin secretion by inhibiting ATP-sensitive potassium channels in pancreatic beta-cells.

Metformin is an oral hypoglycemic agent that improves glycemic control by decreasing hepatic glucose production and intestinal glucose absorption as well as improving insulin sensitivity through increased peripheral glucose uptake and utilization. Alpha glucosidase inhibitors inhibit the ability of alpha glucosidase to convert nonabsorbable dietary starch and sucrose into absorbable glucose, which results in slower glucose absorption and reduced postprandial glucose levels.

The bile acid sequestrant, colesevelam, is FDA-approved for use to manage primary hyperlipidemia as well as type 2 diabetes as an adjunct to diet and exercise. The mechanism by which colesevelam lowers hemoglobin A1c (HbA1c) and improves glycemic control is unknown. Bromocriptine, a dopamine agonist, is FDA-approved as Cycloset® to manage glycemic control in type 2 diabetes as an adjunct to diet and exercise through a currently undetermined mechanism.

The incretin hormones, glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP), have been identified as important factors in glucose homeostasis. Released from the gut postprandially, GLP-1 and GIP stimulate insulin secretion from pancreatic beta cells in response to normal or elevated blood glucose concentrations. GLP-1 also lowers glucagon excretion from pancreatic beta cells, which results in reduced hepatic glucose production, and also reduces appetite, slows gastric emptying, and improves β -cell function. When administered intravenously or subcutaneously, GLP-1 is effective in treating type 2 diabetes. Unfortunately, both GLP-1 and GIP are rapidly degraded by dipeptidyl peptidase IV (DPP-IV); therefore, research has been focused on preventing degradation by inhibiting the DPP-IV enzyme. DPP-IV inhibitors reduce inactivation of incretin hormones and improve glycemic control in type 2 diabetic patients without significant weight gain.

Thiazolidinediones are potent agonists of peroxisome proliferator-activated receptor-gamma (PPAR-gamma), receptors important for insulin action which are located in adipose tissue, liver and skeletal muscle. Activation of these receptors affects the transcription of genes responsible for control of glucose and lipid metabolism. These agents, in the presence of insulin, decrease insulin resistance in the liver and at peripheral sites and improve insulin-dependent glucose disposal and reduce hepatic glucose output.

The thiazolidinediones, rosiglitazone and pioglitazone, have been associated with an increased risk of congestive heart failure most likely due to a greater incidence of fluid retention/edema associated with this drug class. Patients should be closely monitored for signs and symptoms of CHF, and thiazolidinedione dosages reduced or discontinued should symptoms develop. Thiazolidinediones are



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contraindicated for use in NYHA Class III or IV heart failure and are not recommended in patients with symptomatic heart failure.

Recent data have documented an increased risk of heart attack and heart-related deaths in patients prescribed rosiglitazone. The FDA have determined that while the evidence documenting increased cardiovascular ischemic risks with rosiglitazone are not robust or consistent, there are enough areas of concern to warrant significant restrictions on rosiglitazone use. Rosiglitazone is now only approved for use in patients with type 2 diabetes who cannot maintain glycemic control with any other antidiabetic medication.

Female patients treated with thiazolidinediones may be at increased risk for developing fractures. These agents have been shown to stimulate formation of more adipocytes rather than osteoblasts in bone. Thiazolidinediones may also decrease hip and femoral neck bone mineral density in older diabetic patients. Fractures currently reported with thiazolidinedione use have been limited to the humerus, hand and foot in female patients only. Further assessment of thiazolidinedione adverse skeletal effects is necessary to determine the risk-benefit ratio of these agents in diabetic patients. Female patients at higher fracture risk should be considered for bone mineral density assessment and bone strengthening therapies (e.g., calcium, vitamin D, bisphosphonates) prior to therapy initiation with thiazolidinediones.

A new class of medications, sodium-glucose co-transporter 2 (SGLT2) inhibitors, have been developed as additional tools to manage type 2 diabetes. These agents work by inhibiting SGLT2 transporters, which are located in the proximal renal tubule, and reducing reabsorption of filtered glucose which causes increased glucose excretion and lower serum glucose concentrations.

Adults

Maximum recommended daily doses for available oral antidiabetic agents, both as monotherapy and as combination therapy, are summarized in Tables 1 and 2. Prescribed dosages exceeding these recommendations will be reviewed.

TABLE 1: Oral Antidiabetic Agents: Monotherapy - Maximum Recommended Adult Daily Dosages		
Drug	Available Dosage Strengths	Maximum Daily Dosage
ALPHA-GLUCOSIDASE INHIBITORS (AGIs)		
Acarbose (Precose®, generics)	25 mg, 50 mg, 100 mg tablets	patients ≤ 60 kg: 150 mg/day, in three divided doses patients > 60 kg: 300 mg/day, in three divided doses
Miglitol (Glyset®)	25 mg, 50 mg, 100 mg tablets	300 mg/day, in three divided doses
BIGUANIDES		
Metformin immediate-release (Glucophage®, generics)	500 mg, 850 mg, 1000 mg tablets	2550 mg/day
extended-release (Glucophage XR®, Fortamet®, Glumetza®, various generics)	500 mg, 750 mg, 1000 mg tablets	2000 mg/day (2500 mg/day Fortamet®)
oral solution (Riomet®)	500 mg/5ml	2550 mg/day
BILE ACID SEQUESTRANTS		
Colesevelam (Welchol®)	625 mg tablets, 3.75 g powder packet	3.75 g/day, in single or two divided doses



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TABLE 1: Oral Antidiabetic Agents: Monotherapy - Maximum Recommended Adult Daily Dosages (continued)

Drug	Available Dosage Strengths	Maximum Daily Dosage
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS		
Alogliptin (Nesina®, generics)	6.25 mg, 12.5 mg, 25 mg tablets	25 mg/day
Linagliptin (Tradjenta®)	5 mg	5 mg/day
Saxagliptin (Onglyza®)	2.5 mg, 5 mg tablets	5 mg/day
Sitagliptin (Januvia®)	25 mg, 50 mg, 100 mg tablets	100 mg/day
DOPAMINE AGONISTS		
Bromocriptine (Cycloset®)	0.8 mg tablets	4.8 mg/day
MEGLITINIDES		
Nateglinide (Starlix®, generics)	60 mg, 120 mg tablets	360 mg/day, in three divided doses
Repaglinide (Prandin®, generics)	0.5 mg, 1 mg, 2 mg tablets	16 mg/day (in divided doses, up to 4 times daily)
SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS		
Canagliflozin (Invokana®)	100 mg, 300 mg tablets	300 mg/day
Dapagliflozin (Farxiga®)	5 mg, 10 mg tablets	10 mg/day
Empagliflozin (Jardiance®)	10 mg, 25 mg tablets	25 mg/day
SULFONYLUREAS		
Chlorpropamide (various generics)	100 mg, 250 mg tablets	750 mg/day
Glimepiride (Amaryl®, various generics)	1 mg, 2 mg, 4 mg tablets	8 mg/day
Glipizide immediate-release: (Glucotrol®, various generics) extended-release: (Glucotrol XL®, generics)	5 mg, 10 mg tablets 2.5 mg, 5 mg, 10 mg tablets	40 mg/day 20 mg/day
Glyburide nonmicronized (DiaBeta®, various generics) micronized (Glynase®, various generics)	1.25 mg, 2.5 mg, 5 mg tablets 1.5 mg, 3 mg, 6 mg tablets	20 mg/day 12 mg/day
Tolazamide (various generics)	250 mg, 500 mg tablets	1000 mg/day
Tolbutamide (generics)	500 mg tablet	3000 mg/day
THIAZOLIDINEDIONES (TZDs)		
Pioglitazone (Actos®, generics)	15 mg, 30 mg, 45 mg tablets	45 mg/day
Rosiglitazone (Avandia®)	2 mg, 4 mg, 8 mg tablets	8 mg/day



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Table 2: Oral Antidiabetic Agents: Combination Therapy – Maximum Recommended Adult Daily Dosages		
Drug	Available Dosage Strengths	Maximum Daily Dosages
Alogliptin/Metformin (Kazano®)	12.5 mg/500 mg, 12.5 mg/1000 mg tablets	25 mg/2000 mg/day
Alogliptin/Pioglitazone (Oseni®)	12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg tablets	25 mg/45 mg/day
Canagliflozin/Metformin (Invokamet®)	50 mg/500 mg, 50 mg/1000 mg, 150 mg/500 mg, 150 mg/1000 mg tablets	300 mg/2000 mg/day
Dapagliflozin/Metformin (Xigduo® XR)	5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg, 10 mg/1000 mg tablets	10 mg/2000 mg/day
Empagliflozin/Linagliptin (Glyxambi®)	10 mg/5 mg, 25 mg/5 mg tablets	25 mg/5 mg/day
Empagliflozin/Metformin (Synjardy®)	5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, 12.5 mg/1000 mg tablets	25 mg/2000 mg/day
Glipizide/Metformin (generics)	2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg tablets	<i>Diet/exercise alone:</i> 10 mg/2000 mg/day <i>Sulfonylurea and/or metformin:</i> 20 mg/2000 mg/day
Glyburide/ Metformin (Glucovance®, generic)	1.25 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg tablets	<i>Diet/exercise alone:</i> 10 mg/2000 mg/day <i>Sulfonylurea and/or metformin:</i> 20 mg/2000 mg/day
Linagliptin/Metformin immediate-release (Jentadueto®) extended-release (Jentadueto® XR)	2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg tablets 2.5 mg/1000 mg, 5 mg/1000 mg tablets	5 mg/2000 mg/day 5 mg/2000 mg/day
Pioglitazone/Glimepiride (Duetact®, generics)	30 mg/2 mg, 30 mg/4 mg tablets	45 mg/8 mg/day
Pioglitazone/Metformin immediate-release (ActoPlus Met®, generics) extended-release (ActoPlus Met XR®)	15 mg/500 mg, 15 mg/850 mg tablets 15 mg/1000 mg, 30 mg/1000 mg tablets	45 mg/2550 mg/day 45 mg/2000 mg/day
Repaglinide/Metformin (generics)	1 mg /500 mg, 2 mg/500 mg tablets	10 mg/2500 mg/day (4 mg/1000 mg/meal)
Rosiglitazone/Glimepiride (Avandaryl®)*	4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, 8 mg/4 mg tablets	8 mg/4 mg/day



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Table 2: Oral Antidiabetic Agents: Combination Therapy – Maximum Recommended Adult Daily Dosages (continued)

Drug	Available Dosage Strengths	Maximum Daily Dosages
Rosiglitazone/Metformin (Avandamet®)*	2 mg/500 mg, 2 mg/1000 mg, 4 mg/500 mg, 4 mg/1000 mg tablets	8 mg/2000 mg/day
Saxagliptin/Metformin (Kombiglyze XR®)	5 mg/500 mg, 2.5 mg/1000 mg, 5 mg/1000 mg tablets	5 mg/2000 mg/day
Sitagliptin/Metformin immediate-release (Janumet®) extended-release (Janumet XR®)	50 mg/500 mg, 50 mg/1000 mg tablets 50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg tablets	100 mg/2000 mg/day

*available only through specialty pharmacies due to concerns for cardiovascular safety

Pediatrics

Oral sulfonylureas, alpha-glucosidase inhibitors, pioglitazone, meglitinides, DPP-4 inhibitors, and SGLT2 inhibitors are not FDA-approved for use in pediatric patients as safety and efficacy have not been determined in this patient population. Sufficient data are not available to assess rosiglitazone safety and efficacy in pediatric patients.

Metformin immediate-release is FDA-approved for use in pediatric type 2 diabetic patients 10 years of age and older as an adjunct to diet in exercise to aid in controlling blood glucose. Maximum recommended oral antidiabetic doses in pediatric patients are summarized in Table 3. Dosages exceeding these recommendations will be reviewed.

Table 3: Recommended Oral Antidiabetic Agent Daily Doses in Pediatric Patients	
Drug	Maximum Recommended Dosage
<i>Monotherapy</i>	
Metformin immediate-release:	≥ 10 years of age: 2000 mg/day, in divided doses

Renal Impairment

Metformin should be used cautiously in patients with creatinine clearance (CrCl) < 60 ml/min. Renal function should be closely monitored in patients with CrCl of 30-59 ml/min, with doses decreased by 50% in patients with CrCl of 30-44 ml/min. Metformin doses should be discontinued in patients with CrCl < 30 ml/min; the manufacturer recommends discontinuing metformin in women or men with a serum creatinine > 1.4 mg/dL or 1.5 mg/dL, respectively. Lower glyburide doses (e.g., 1.25 mg daily – conventional tablets; 0.75 mg daily – micronized tablets) should be initiated in patients with renal dysfunction to minimize hypoglycemic events. Sitagliptin dosages should be adjusted in adult patients with renal insufficiency. Patients with moderate renal insufficiency (CrCl ≥ 30 to < 50 ml/min corresponding to serum creatinine levels between 1.7 and 3 mg/dl in men and 1.5 and 2.5 mg/dl in women) should receive sitagliptin 50 mg daily, while patients with severe renal insufficiency (CrCl < 30 ml/min corresponding to serum creatinine levels in men > 3 mg/dl or > 2.5 mg/dl in women) or those patients with end stage renal disease requiring hemodialysis or peritoneal dialysis should receive sitagliptin 25 mg daily. Saxagliptin dosages should be reduced to 2.5 mg once daily in patients with CrCl < 50 ml/min or in patients prescribed a strong CYP3A4 inhibitor (e.g., ketoconazole). Linagliptin dosages do not need to be adjusted for renal insufficiency. Patients on linagliptin combination therapy with a CrCl < 30 ml/min may have increased risk of hypoglycemia and may need more frequent monitoring and/or dose adjustments. In moderate renal impairment (CrCl 30 to < 60 ml/min), alogliptin dosages should be reduced to 12.5 mg daily, while in patients with severe renal impairment (CrCl 15 to < 30 ml/min), alogliptin dosages should not exceed 6.25 mg daily. Canagliflozin doses in patients with renal impairment should be reduced to 100 mg daily when the glomerular filtration rate



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(GFR) is 45-59 ml/min/1.73 m² and avoided completely when GFR is < 45 ml/min/1.73 m². Dapagliflozin therapy is not recommended for use in patients with GFR < 60 ml/min/1.73 m². Empagliflozin therapy should not be initiated in patients with GFR < 45 ml/min/1.73m² and should be discontinued in those patients who develop impaired renal function (GFR < 45 ml/min/1.73 m²).

2. Duration of Therapy

There is no basis for limiting the duration of oral antidiabetic therapy as diabetes is a chronic disorder.

3.* Duplicative Therapy

Administering two or more oral sulfonylureas concurrently is not justified. The concomitant use of two or more oral sulfonylureas will be reviewed.

Combined administration of nateglinide or repaglinide and oral sulfonylureas is not justified as both drug classes stimulate insulin secretion. Adjunctive use of meglitinides and oral sulfonylureas will be reviewed.

The risk of hypoglycemia may increase when acarbose or miglitol is added to pre-existing oral hypoglycemic or insulin therapy. Blood glucose levels should be monitored closely when alpha glucosidase inhibitor therapy is initiated in patients already receiving oral hypoglycemic or insulin therapy.

Adjunctive administration of rosiglitazone and insulin is not recommended as a greater incidence of myocardial ischemic events was observed in clinical trials when rosiglitazone was added to insulin therapy.

Concurrent administration of thiazolidinediones or metformin with sulfonylureas may result in an increased frequency of hypoglycemic episodes. Blood glucose levels should be closely monitored if patients are prescribed thiazolidinediones or metformin and oral sulfonylureas concomitantly, and oral sulfonylurea dosage reductions should be considered.

Concurrent administration DDP-4 inhibitors and sulfonylureas, with or without metformin, have resulted in significant reductions in HbA1c and fasting plasma glucose compared to placebo. The risk of hypoglycemia with DDP-4 inhibitors in combination with metformin and TZDs is comparable to that observed with placebo; however the incidence of hypoglycemia in patients prescribed DDP-4 inhibitors concurrently with sulfonylureas is greater than that seen with placebo. The incidence of hypoglycemia in patients prescribed DDP-4 inhibitors and insulin concurrently has not been adequately evaluated. Therefore, blood glucose levels should be closely monitored if patients are prescribed DDP-4 inhibitors and oral sulfonylureas or insulin concomitantly, and oral sulfonylurea dosage reductions should be considered.

Concomitant use of multiple SGLT2 inhibitors is not recommended due to similar pharmacologic mechanisms and increased risk of adverse events. **Combined administration is not advised and will be reviewed.**

4.* Drug-Drug Interactions

Patient profiles will be reviewed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for oral antidiabetic agents are summarized in Table 4. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:



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Table 4: Oral Antidiabetic Agent Drug-Drug Interactions

TARGET DRUG	INTERACTING DRUG	INTERACTION	RECOMMENDATIONS	SIGNIFICANCE LEVEL *
acarbose	digoxin	adjunctive administration may result in decreased digoxin levels; acarbose most likely impairs digoxin absorption	avoid concurrent administration; separate administration by 6 hours to avoid interaction; monitor digoxin levels	2-major (CP)
alpha-glucosidase inhibitors (AGIs)	digestive enzymes	combined therapy may result in decreased AGI absorption, reduced pharmacologic effects	avoid concurrent administration	moderate (DrugReax) 2-major (CP)
antidiabetic agents (ADAs)	ACE inhibitors/angiotensin receptor blockers (ARBs)	combined therapy may result in increased risk of hypoglycemia, most likely due to ACE inhibitor/ARB improved insulin sensitivity	monitor glycemic control when initiating or changing therapy	3-moderate (CP)
ADAs	atypical antipsychotics (AAs)	combined therapy may result in loss of glycemic control; AAs may increase insulin resistance or inhibit beta cells	monitor for loss of glycemic control; adjust doses as necessary	3-moderate (CP)
ADAs	beta blockers (BB)	BB may prolong hypoglycemia (interference with mobilization of glycogen stores), promote hyperglycemia (inhibit insulin secretion/decrease tissue insulin sensitivity), as well as mask signs/symptoms of hypoglycemia	administer cautiously together; consider cardioselective BB due to lesser effects on glucose metabolism, less masking of hypoglycemic signs/symptoms	moderate (DrugReax) 3-moderate (CP)
ADAs	fluoroquinolones	combined administration may increase risk of hyper- or hypoglycemia; mechanism unknown	closely monitor serum glucose levels; adjust ADA doses as needed	major (DrugReax) 3-moderate (CP)
ADAs	MAOIs	adjunctive therapy may result in additive glucose-lowering effects; MAOIs may stimulate insulin secretion	closely monitor serum glucose levels; decrease antidiabetic agent doses as necessary	moderate (DrugReax) 3-moderate (CP)
ADAs	thiazide diuretics	combined therapy may antagonize hypoglycemic effects of ADAs as thiazides increase blood glucose levels in dose-related manner	utilize lower thiazide doses, if possible; monitor serum glucose levels; adjust ADA doses as needed	3-moderate (CP)
bromocriptine	ergot alkaloids	combined therapy may increase risk of ergot toxicity (e.g., angina, paresthesias) as bromocriptine is ergot derivative	avoid using together	1-severe (CP)



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Table 4: Oral Antidiabetic Agent Drug-Drug Interactions (continued)				
Target Drug	Interacting Drug	Interaction	Recommendation	Significance Level*
bromocriptine	metoclopramide	combined therapy may attenuate bromocriptine pharmacological effects; metoclopramide is dopamine antagonist	avoid concurrent use	2-major (CP)
bromocriptine	select macrolides (e.g., clarithromycin, erythromycin)	potential for increased bromocriptine pharmacologic/adverse effects due to decreased hepatic metabolism by macrolide	monitor patient for adverse effects; decrease bromocriptine dose as necessary	moderate (DrugReax) 3-moderate (CP)
bromocriptine	serotonin-receptor agonists (e.g., sumatriptan)	increased risk of serious coronary ischemia due to potential for additive vasospasm	avoid concurrent administration within 24 hours of each other	2-major (CP)
bromocriptine	drugs metabolized by CYP3A4 (e.g., tacrolimus, cyclosporine, sirolimus)	potential for decreased cyclosporine/sirolimus/tacrolimus clearance, enhanced pharmacologic/adverse effects; bromocriptine is CYP3A4 inhibitor	monitor for increased pharmacologic/adverse effects; consider reducing dose of CYP3A4 substrate	2-major (CP)
canagliflozin	UGT enzyme inducers (e.g., rifampin)	adjunctive administration may decrease canagliflozin AUC by 51% and reduce therapeutic efficacy as canagliflozin is metabolized through O-glucuronidation by several UGT enzymes (UGT1A9 and UGT2B4)	administer cautiously together; may increase canagliflozin dose to 300 mg daily during adjunctive therapy with UGT enzyme inducers or may consider alternative antidiabetic agents metabolized by different mechanisms	major (DrugReax) 2-major (CP)
colesevelam	cyclosporine	decreased cyclosporine peak serum concentrations and AUC with combined therapy	administer cyclosporine at least 4 hours prior to colesevelam; monitor serum cyclosporine levels	3-moderate (CP)
colesevelam	oral contraceptives (OC)	decreased peak ethinyl estradiol/norethindrone serum levels, AUC with combined therapy	administer OC at least 4 hours before colesevelam	3-moderate (CP)
colesevelam	thyroid hormones (TH) (e.g., levothyroxine, liothyronine)	combined therapy may cause reduced thyroid hormone absorption due to nonspecific binding to colesevelam	take TH at least 4 hours prior to colesevelam; monitor for adequate thyroid response; adjust TH dose as needed	moderate (DrugReax) 3-moderate (CP)



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Table 4: Oral Antidiabetic Agent Drug-Drug Interactions (continued)

Target Drug	Interacting Drug	Interaction	Recommendations	Significance Level*
glimepiride	voriconazole	combined therapy may increase glimepiride levels and risk of hypoglycemia; voriconazole inhibits CYP2C9, glimepiride metabolized by CYP2C9	monitor for hypoglycemia; consider lowering glimepiride dose	major (DrugReax) 3-moderate (CP)
glyburide, TZDs	bosentan	increased risk of elevated liver enzymes when used concurrently; bosentan, a CYP2C9 and CYP3A4 inducer, may decrease glyburide and TZD levels/reduce hypoglycemic effects; glyburide, rosiglitazone metabolized by CYP2C9, pioglitazone metabolized by CYP3A4	combined therapy contraindicated; choose alternative ADA	glyburide -1-severe; TZDs - 2-major (CP) glyburide - contraindicated (DrugReax)
linagliptin	CYP3A4 and p-glycoprotein inducers	combined therapy may significantly decrease linagliptin concentrations decrease efficacy; linagliptin metabolized by CYP3A4	administer cautiously together; monitor serum glucose levels	rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, St. John's wort - major (DrugReax) others - moderate (DrugReax)
meglitinides, sulfonylureas, TZDs	rifamycins	combined therapy may result in reduced ADA serum levels and loss of hypoglycemic control due to enhanced ADA hepatic metabolism by rifamycin	closely monitor serum glucose levels; adjust ADA dose as necessary	moderate (DrugReax) 4-minor (CP)
metformin	dofetilide	increased risk of lactic acidosis; dofetilide decreases metformin elimination by competing for renal tubular transport system; potential for increased dofetilide serum concentrations and cardiotoxicity risk	manufacturer recommends avoiding concurrent use	1-severe (CP) major (DrugReax)
pioglitazone	estrogens, progestins, OCs	combined therapy may attenuate pioglitazone hypoglycemic effects; estrogens, progestins, OCs impair glucose tolerance; also, pioglitazone lowers estrogen levels when used as combined therapy with OCs, potentially resulting in reduced OC effectiveness	monitor for changes in glycemic control; may consider higher dose OC or alternative form of contraception	2-major (CP)



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Table 4: Oral Antidiabetic Agent Drug-Drug Interactions (continued)				
Target Drug	Interacting Drug	Interaction	Recommendations	Significance Level*
pioglitazone	tolvaptan	combined therapy may decrease tolvaptan concentrations; pioglitazone is CYP3A4 inducer, tolvaptan is metabolized by CYP3A4	avoid concurrent use if possible; if combined therapy necessary, increase tolvaptan dose and monitor efficacy	major (DrugReax)
repaglinide, TZDs	gemfibrozil	combined therapy increases potential for elevated repaglinide or TZD levels/amplified repaglinide or TZD hypoglycemic effects due to gemfibrozil inhibition of CYP2C8; repaglinide, TZDs metabolized by CYP2C8	avoid concurrent administration; if combination cannot be avoided, use lower repaglinide dose	contraindicated (DrugReax) 1-severe (CP)
repaglinide	CYP3A4 inhibitors (e.g., rifamycins, macrolides, itraconazole)	combined therapy may significantly increase repaglinide concentrations and increase hypoglycemia risk; repaglinide metabolized by CYP3A4	administer cautiously together; monitor for hypoglycemia; adjust repaglinide dose as necessary	itraconazole-major ; others – moderate (DrugReax) 2-major (CP)
repaglinide	cyclosporine	cyclosporine is CYP3A4 inhibitor, also inhibits uptake of repaglinide into liver by inhibiting OATP1B1, which increases risk of elevated repaglinide levels and hypoglycemia when given concurrently	administer cautiously together; closely monitor glycemic control; adjust repaglinide dose as necessary	2-major (CP)
repaglinide	isophane insulin (NPH)	combined therapy caused myocardial ischemia in clinical trials	avoid concurrent administration	2-major (CP)
rosiglitazone	nitrates	in clinical trials, increased risk of myocardial ischemia in patients receiving combined therapy	avoid concurrent administration (manufacturer recommendations)	2-major (CP)
saxagliptin	CYP3A4/5 inhibitors (e.g., ketoconazole, erythromycin, fluconazole)	combined therapy may increase saxagliptin levels and risk of hypoglycemia; saxagliptin metabolized by CYP3A4/5	utilize lower saxagliptin dose (2.5 mg daily) with strong CYP3A4/5 inhibitors (e.g., ketoconazole); adjunctive therapy with moderate CYP3A4/5 inhibitors does not warrant dosage adjustments	2-major (CP)
sulfonylureas	methotrexate	concurrent administration may result in methotrexate displacement from protein binding sites and increased risk of methotrexate toxicity	consider avoiding combination; watch for signs of toxicity	2-major (CP)



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Table 4: Oral Antidiabetic Agent Drug-Drug Interactions (continued)				
Target Drug	Interacting Drug	Interaction	Recommendations	Significance Level*
sulfonylureas	sulfonamides	combined therapy may exaggerate sulfonylurea hypoglycemic effects; sulfonamides may inhibit sulfonylurea metabolism or displace sulfonylurea from protein binding site; glipizide, glyburide not significantly affected due to nonionic binding of these agents	use combination cautiously; closely monitor serum glucose levels, observe for signs/symptoms of hypoglycemia, reduce sulfonylurea dose as necessary	moderate (DrugReax) 3-moderate (CP)
tolbutamide	CYP2C9 inhibitors (e.g., imatinib, sorafenib, delavirdine)	combined therapy may increase tolbutamide serum concentrations, increase risk of hypoglycemia	closely monitor serum glucose levels	2-major (CP)
TZDs	insulins	combined therapy associated with increased risk of heart failure and/or edema and myocardial ischemic events	manufacturer recommends avoiding concurrent use	2-major (CP)

*CP = Clinical Pharmacology

ACE = angiotensin converting enzyme; MAOIs = monoamine oxidase inhibitors; TZD = thiazolidinedione; UGT = UDP-glucuronosyltransferase



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Prepared by: Drug Information Service, The University of Texas Health Science Center at San Antonio, and the College of Pharmacy, The University of Texas at Austin.