Table 1. Antihyperglycemic agents for use in type 2 diabetes

CLASS* AND MECHANISM OF ACTION	DRUG (BRAND NAME)	EXPECTED† DECREASE IN A1C	RELATIVE† A1C LOWERING	HYPOGLYCEMIA	OTHER THERAPEUTIC CONSIDERATIONS
Alpha-glucosidase inhibitor: inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase	acarbose (Glucobay) (7,81,82)	0.6%	↓	Negligible risk as monotherapy	• Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥ 8.5%) • Weight neutral as monotherapy • GI side effects
Combined formulations	Avandamet (metformin + rosiglitazone)	0.8%	↓↓	Negligible risk as monotherapy	See metformin, TZDs, DPP-4 inhibitors, and sulfonylureas
	Avandaryl (glimepiride + rosigltizaone)	1.6%	↓↓↓	Moderate risk	
	Janumet/Janumet XR (metformin/metformin ER + sitagliptin)	0.7%	↓↓	Negligible risk as monotherapy	
	Jentadueto (linagliptin + metformin)	0.7%	↓↓	Negligible risk as monotherapy	
	Kazano (alogliptin + metformin)	0.7%	↓↓	Negligible risk as monotherapy	
	Komboglyze (metformin + saxagliptin)	0.7%	↓↓	Negligible risk as monotherapy	
	Oseni (alogliptin + pioglitzone)	1.5%	↓↓↓	Negligible risk as monotherapy	
DPP-4 inhibitor: amplifies incretin pathway activation by inhibition of enzymatic breakdown of endogenous GLP-1 and GIP *(45, Product monograph – Nesina- Nov 7, 2014)*	Alogliptin (Nesina)	0.7%	↓↓	Negligible risk as monotherapy	• Weight neutral • Improved post-prandial control • Rare cases of pancreatitis
	Linagliptin (Trajenta)				
	Sitagliptin (Januvia)				
	Saxagliptin (Onglyza)				
GLP-1 receptor agonist: activates incretin pathway by utilizing DPP-4 resistant analogue to GLP-1 *(45-48. Product monograph – Eperzan - July 15, 2015)*	Albiglutide (Eperzan)	1.0%	↓↓ to ↓↓↓	Negligible risk as monotherapy	• Improved postprandial control • Significant weight loss • Nausea and vomiting • Administration parenteral • Rare cases of pancreatitis • Parafollicular cell hyperplasia • Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
	Exenatide (Byetta)				
	Liraglutide (Victoza)				

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Insulin: activates insulin receptors to regulate metabolism of carbohydrate, fat, and protein *(3,10,11,50,53,83 – 85, Product monograph-Toujeo – May 28, 2015.)*	**Bolus (prandial) Insulins** **Rapid-acting analogues** Aspart (NovoRapid) Glulisine (Apidra) Lispro (Humalog) **Short-acting** Regular (Humulin-R, Novolin geToronto) (Note: Pork regular insulin (Hypurin Regular Insulin Pork) and pork isophane insulin (Hypurin NPH Insulin Isophane) are available but rarely used)	0.9 – 1.1%	↓↓↓	Significant risk risk highest with regular and NPH insulin)	• Potentially greatest A1C reduction and no maximal dose • Numerous formulations and delivery systems (including subcutaneous-injectable) • Allows for regimen flexibility • When initiating insulin, consider adding bedtime long-acting basal analogue or intermediate-acting NPH to daytime oral antihyperglycemic agents (although other regimens can be used) • Basal-bolus regimen recommended if above fails to attain glycemic targets • Increased risk of weight gain relative to sulfonylureas and metformin
	Basal Insulins **Intermediate-acting** NPH (Humulin-N, Novolin ge NPH) **Long-acting basal analogues** Detemir (Levemir) Glargine (Lantus) Glargine U300 (Toujeo) (Note: Pork isophane insulin [Hypurin NPH Insulin Isophane] is available but rarely used)				
	Premixed Insulins Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) Biphasic insulin aspart (NovoMix 30) Insulin lispro/lispro protamine suspension (Humalog Mix25, Mix50)				

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Insulin secretagogue: activates sulfonylurea receptor on beta cell to stimulate endogenous insulin secretion	**Sulfonylureas** Gliclazide (Diamicron, Diamicron MR, generic) (86,87)	0.8%	↓↓	Minimal/ moderate risk	• Relatively rapid BG-lowering response • All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective) • Post-prandial glycemia is especially reduced by meglitinides • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure) • If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia (94) and glimepiride is associated with less hypoglycemia than glyburide (90) • Nateglinide and repaglinide are associated with less hypoglycemia than sulfonylureas due to their shorter duration of action allowing medication to be held when forgoing a meal
	Glimepiride (Amaryl) (88,89,90)			Moderate risk	
	Glyburide (Diabeta, Euglucon, generic) (3) (Note: Chlorpropamide and Tolbutamide are available but rarely used)			Significant risk	
	Meglitinides nateglinide (Starlix) (91)	0.7%	↓	Minimal/moderate risk	
	repaglinide (GlucoNorm) (92,93)		↓↓		
Metformin: enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase	Glucophage, Glumetza, generic (52,95)	1.0 – 1.5%	↓↓	Negligible risk as monotherapy	• Improved cardiovascular outcomes in overweight subjects • Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure • Caution if CrCl/eGFR <60 mL/min • Weight neutral as monotherapy, promotes less weight gain when combined with other antihyperglycemic agents, including insulin • B12 deficiency (96) • GI side effects

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Sodium-glucose linked transporter 2 (SGLT2) inhibitor: enhances urinary glucose excretion by inhibiting glucose reabsorption in the proximal renal tubule *(Harper W, Clement M, Goldenberg R, et al. On behalf of The Steering Committee for the Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes, Policies Guidelines and Consensus Statements: Pharmacologic Management of Type 2 Diabetes – 2015 Interim Update, Can J Diabetes 2015; 39: 250-252.* *Product monograph – Invokana – Nov 7, 2014. Product monograph – Forxiga – Dec 10, 2014. Product monograph – Jardiance – July 21, 2015)*	Canagliflozin (Invokana) Dapagliflozin (Forxiga) Empagliflozin (Jardiance)	0.7 – 1.0%	↓↓ to ↓↓↓	Negligible risk as monotherapy	• UTI, Genital infections, • Hypotension, caution with concomitant loop diuretic use • Caution with renal dysfunction • Hyperlipidemia (raises LDL-C and HDL-C) • Dapagliflozin not be used in patients with active or history of bladder cancer • Rare diabetic ketoacidosis (may occur with no hyperglycemia)

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Thiazolidinedione (TZD): enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator-activated receptor-gamma receptors *(28 – 30,33,35 97 – 104)*	Pioglitazone (Actos) Rosiglitazone (Avandia)	0.8%	↓↓	Negligible risk as monotherapy	• Longer duration of glycemic control with monotherapy compared to metformin or glyburide • Mild BP lowering • Between 6 and 12 weeks required to achieve full glycemic effect • Weight gain • May induce edema and/or congestive heart failure • Contraindicated in patients with known clinical heart failure or evidence of left ventricular dysfunction on echocardiogram or other heart imaging • Higher rates of heart failure when combined with insulin‡ • Rare occurrence of macular edema • Higher occurrence of fractures (29,30,33) • Possibility of increased risk of myocardial infarction with rosiglitazone (31,108) • Rare risk bladder cancer with pioglitazone (109)
Weight loss agent: inhibits lipase	Orlistat (Xenical) (105 – 107,110)	0.5%	↓	None	• Promote weight loss • Orlistat can cause diarrhea and other GI side effects

A1C, glycated hemoglobin; **BG,** blood glucose; **BP,** blood pressure; **CrCl,** creatinine clearance; **DPP-4,** dipeptidyl peptidase 4; **eGFR,** estimated glomerular filtration rate; **GI,** gastrointestinal; **GIP,** gastric inhibitory peptide; **GLP-1,** glucagon-like peptide 1; **AMP,** adenosine monophosphate.

Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and detailed prescribing information.

* Listed in alphabetical order.

† A1C percentage/relative reduction expected when agent from this class is added to metformin therapy (37,105,111) with exception of metformin where A1C percentage/relative reduction reflects expected monotherapy efficacy.

‡ Combining insulin with a TZD is not an approved indication in Canada.