

Appendix F. Table of evidence and properties of glucose-lowering agents

Refer to Figure 4 for more information.

Glucose-lowering class and drugs	Mechanism of action	Outcome data	Contraindications	
Biguanide <ul style="list-style-type: none">• metformin• metformin XR	Reduces hepatic glucose output, lowers fasting glucose levels	UKPDS ¹	Renal impairment (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m ²) Severe hepatic impairment	
Sulphonylureas <ul style="list-style-type: none">• glibenclamide• gliclazide• gliclazide modified release (MR)• glimepiride• glipizide	Triggers insulin release in a glucose-independent manner	UKPDS ^{2,3}	Severe renal or hepatic impairment	
Dipeptidyl peptidase-4 inhibitors (DPP-4i) <ul style="list-style-type: none">• alogliptin• linagliptin• saxagliptin• sitagliptin• vildagliptin	Decreases inactivation of glucagon-like peptide 1 (GLP-1) thereby increasing its availability GLP-1 stimulates beta cell insulin release and slows gastric emptying	EXAMINE ^{4,5} – Alogliptin SAVOR-TIMI 53 ^{6,7} – Saxagliptin TECOS ⁸ – Sitagliptin	Pancreatitis ⁹	
Thiazolidinediones (TZD) <ul style="list-style-type: none">• pioglitazone• rosiglitazone	Transcription factor peroxisome proliferator-activated receptor PPAR γ agonists Lowers glucose levels through insulin sensitisation	PROACTIVE ¹¹ – Pioglitazone		

	Precautions, side effects and administration	Cost and accessibility
	<p>Precautions Suspend treatment during acute disease/conditions with the potential to cause tissue hypoxia or alter renal function.</p> <p>Side effects Gastrointestinal side effects, lactic acidosis, weight neutral</p> <p>Administration Oral administration Start at low dose and up-titrate Slow release preparations available</p>	<p>General schedule on Pharmaceutical Benefits Scheme (PBS)</p>
	<p>Precautions Hypoglycaemia</p> <p>Side effects Weight gain</p> <p>Administration Oral administration Start at low dose and up-titrate Slow release preparation available</p>	<p>General schedule on PBS</p>
	<p>Precautions Nasopharyngitis – often subsides in 10–14 days</p> <p>Side effects Rash, pancreatitis, gastrointestinal disturbances, weight neutral</p> <p>Administration Oral administration Dosage adjustment in renal impairment (except Linagliptin)¹⁰</p>	<p>Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin:</p> <ul style="list-style-type: none"> • PBS-subsidised for use in combination with metformin and sulphonylureas or both* • Linagliptin and sitagliptin will be listed on the PBS from October 2016 to be used in combination with insulin
	<p>Precautions Symptomatic heart failure</p> <p>Side effects Fluid retention, heart failure, increased risk of non-axial fractures in women, increased risk of bladder cancer, weight gain</p> <p>Administration Oral administration</p>	<p>PBS-subsidised for use in combination with metformin, sulphonylurea or both</p> <p>Patient must have a contraindication or intolerance to metformin-sulphonylurea combination</p> <p>PBS-subsidised for use with insulin</p>

Table of evidence and properties of glucose-lowering agents – Continued

Glucose-lowering class and drugs	Mechanism of action	Outcome data	Contraindications	
Alpha 1 glucosidase inhibitors <ul style="list-style-type: none">• acarbose	Slows intestinal carbohydrate absorption and reduces postprandial glucose levels		Severe renal impairment (creatinine clearance <25 mL/min/m ²)	
Sodium-glucose co-transporter-2 (SGLT2) inhibitors <ul style="list-style-type: none">• canagliflozin• dapagliflozin• empagliflozin	Inhibits a sodium-glucose co-transporter to produce urinary glucose loss and decrease glucose levels	EMPA-REG OUTCOME¹² – Empagliflozin	Diminished efficacy with renal impairment (eGFR <60 mL/min/1.73 m ²)	
Glucagon-like peptide-1 receptor agonist (GLP-1 RA) <ul style="list-style-type: none">• exenatide• exenatide ER• liraglutide• lixisenatide	Stimulates beta-cell insulin release and slows gastric emptying	ELIXA^{13,14} – Lixisenatide LEADER¹⁵ – Liraglutide	Avoid with history of pancreatitis or pancreatic malignancy	
Insulin	Directly activates the insulin receptor	UKPDS²		

¹Saxagliptin and sitagliptin are currently PBS listed for triple oral therapy, linagliptin and vildagliptin have been recommended by PBAC for triple oral therapy (date is not yet available)

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	Precautions, side effects and administration	Cost and accessibility
	<p>Precautions GI disorders associated with malabsorption</p> <p>Side effects Bloating and flatulence, weight neutral</p> <p>Administration Oral administration Take with meals as tolerated</p>	<p>General schedule on PBS</p>
	<p>Precautions Avoid use with loop diuretics</p> <p>Side effects Dehydration, dizziness, genitourinary infections (advise adequate fluid intake and meticulous toileting hygiene), ketoacidosis, weight loss</p> <p>Administration Oral administration</p>	<p>Dapagliflozin and empagliflozin:</p> <ul style="list-style-type: none"> • PBS-subsidised for use in combination with metformin, sulphonylurea or both • PBS-subsidised for use with insulin <p>Not PBS-subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1</p> <p>Canagliflozin: PBS-subsidisation withdrawn</p>
	<p>Precautions Dosage adjustment in moderate-severe renal impairment Increased risk of pancreatitis</p> <p>Side effects Nausea, vomiting, weight loss</p> <p>Administration Subcutaneous injection</p>	<p>Exenatide and exenatide ER:</p> <ul style="list-style-type: none"> • PBS-subsidised for use in combination with metformin, sulphonylurea or both • Exenatide • PBS-subsidised for use with insulin <p>Not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or an SGLT2 inhibitor</p> <p>Liraglutide: not PBS-subsidised</p>
	<p>Precautions Consider need for dosage adjustment in moderate-severe renal disease</p> <p>Side effects Hypoglycaemia, weight gain</p> <p>Administration Subcutaneous injection Considered early if blood glucose level (BGL) is very high</p>	<p>General schedule on PBS</p> <p>Levemir insulin: PBS-subsidisation restricted to type 1 Diabetes</p>

References – Appendix F

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