

## 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
<b>Biguanide</b> <ul style="list-style-type: none"><li>metformin</li><li>metformin XR</li></ul>	Reduces hepatic glucose output, lowers fasting glucose levels	UKPDS <sup>1</sup>	Renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m <sup>2</sup> ) Severe hepatic impairment
<b>Sulphonylureas</b> <ul style="list-style-type: none"><li>glibenclamide</li><li>gliclazide</li><li>gliclazide modified release (MR)</li><li>glimepiride</li><li>glipizide</li></ul>	Triggers insulin release in a glucose-independent manner	UKPDS <sup>2,3</sup>	Severe renal or hepatic impairment
<b>Dipeptidyl peptidase-4 inhibitors</b> (DPP-4i) <ul style="list-style-type: none"><li>alogliptin</li><li>linagliptin</li><li>saxagliptin</li><li>sitagliptin</li><li>vildagliptin</li></ul>	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 <sup>4,5</sup> – Alogliptin <b>SAVOR-TIMI 53</b> <sup>6,7</sup> – Saxagliptin <b>TECOS</b> <sup>8</sup> – Sitagliptin	Pancreatitis <sup>9</sup>
<b>Thiazolidinediones (TZD)</b> <ul style="list-style-type: none"><li>pioglitazone</li><li>rosiglitazone</li></ul>	Transcription factor peroxisome proliferator-activated receptor PPAR $\gamma$ agonists  Lowers glucose levels through insulin sensitisation	<b>PROACTIVE</b> <sup>11</sup> – Pioglitazone	

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

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 • acarbose	Slows intestinal carbohydrate absorption and reduces postprandial glucose levels		Severe renal impairment (creatinine clearance <25 mL/min/m <sup>2</sup> )
Sodium-glucose co-transporter-2 (SGLT2) inhibitors • canagliflozin • dapagliflozin • empagliflozin	Inhibits a sodium-glucose co-transporter to produce urinary glucose loss and decrease glucose levels	EMPA-REG OUTCOME <sup>12</sup> – Empagliflozin	Diminished efficacy with renal impairment (eGFR <60 mL/min/1.73 m <sup>2</sup> )
Glucagon-like peptide-1 receptor agonist (GLP-1 RA) • exenatide • exenatide ER • liraglutide • lixisenatide	Stimulates beta-cell insulin release and slows gastric emptying	ELIXA <sup>13,14</sup> – Lixisenatide  LEADER <sup>15</sup> – Liraglutide	Avoid with history of pancreatitis or pancreatic malignancy
Insulin	Directly activates the insulin receptor	UKPDS <sup>2</sup>	

<sup>2</sup>Saxagliptin 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)

Reproduced with permission from the Australian Diabetes Society.

	Precautions, side effects and administration	Cost and accessibility
	<p><b>Precautions</b> GI disorders associated with malabsorption</p> <p><b>Side effects</b> Bloating and flatulence, weight neutral</p> <p><b>Administration</b> Oral administration Take with meals as tolerated</p>	General schedule on PBS
	<p><b>Precautions</b> Avoid use with loop diuretics</p> <p><b>Side effects</b> Dehydration, dizziness, genitourinary infections (advise adequate fluid intake and meticulous toileting hygiene), ketoacidosis, weight loss</p> <p><b>Administration</b> Oral administration</p>	<p>Dapagliflozin and empagliflozin:</p> <ul style="list-style-type: none"> <li>• PBS-subsidised for use in combination with metformin, sulphonylurea or both</li> <li>• PBS-subsidised for use with insulin</li> </ul> <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><b>Precautions</b> Dosage adjustment in moderate-severe renal impairment Increased risk of pancreatitis</p> <p><b>Side effects</b> Nausea, vomiting, weight loss</p> <p><b>Administration</b> Subcutaneous injection</p>	<p>Exenatide and exenatide ER:</p> <ul style="list-style-type: none"> <li>• PBS-subsidised for use in combination with metformin, sulphonylurea or both</li> <li>• Exenatide</li> <li>• PBS-subsidised for use with insulin</li> </ul> <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><b>Precautions</b> Consider need for dosage adjustment in moderate-severe renal disease</p> <p><b>Side effects</b> Hypoglycaemia, weight gain</p> <p><b>Administration</b> 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

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352(9131):854–65.
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352(9131):837–53.
3. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–72.
4. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–35.
5. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: A multicentre, randomised, double-blind trial. *Lancet* 2015;385(9982):2067–76.
6. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–26.
7. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: Observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014;130(18):1579–88.
8. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373(3):232–42.
9. Meier JJ, Nauck MA. Risk of pancreatitis in patients treated with incretin-based therapies. *Diabetologia* 2014;57(7):1320–24.
10. McGill JB, Sloan L, Newman J, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: A 1-year, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2013;36(2):237–44.
11. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): A randomised controlled trial. *Lancet* 2005;366(9493):1279–89.
12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373(22):2117–28.
13. Diaz R, McMurray JV, Lewis EF, et al. The evaluation of lixisenatide in acute coronary syndrome – The results of ELIXA symposium. Boston, MA: 75th Scientific Sessions of the American Diabetes Association, 2015.
14. Bentley-Lewis R, Aguilar D, Riddle MC, et al. Rationale, design, and baseline characteristics in evaluation of lixisenatide in acute coronary syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo. *Am Heart J* 2015;169(5):631–38.e7.
15. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375(4):311–22.