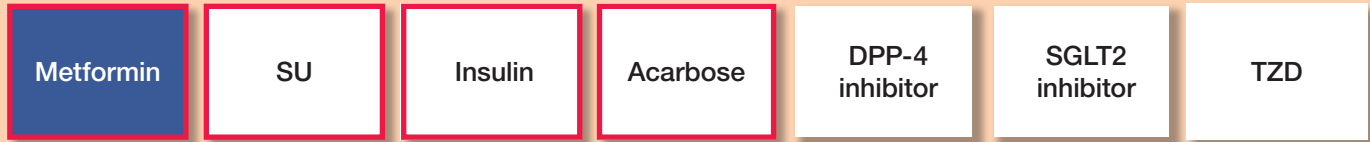


AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

All patients should receive education regarding lifestyle measures: healthy diet, physical activity and weight control
 Determine the individual's HbA_{1c} target – this will commonly be ≤ 53 mmol/mol (7.0%).
 If not at target, or if an HbA_{1c} reduction of ≥ 0.5% is not achieved after 3 months, move down the algorithm.

First line: Metformin is the usual first-line therapy unless contraindicated or not tolerated

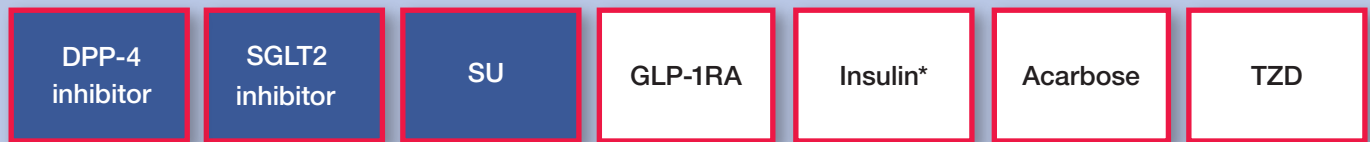


If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

Second line: If metformin was not used first line, add it now, if not contraindicated.

Choice of second line agent to add to metformin should be guided by clinical factors/considerations, contraindications, side effect profile and cost.



If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

Third line: Consider triple oral therapy or addition of GLP-1RA or insulin

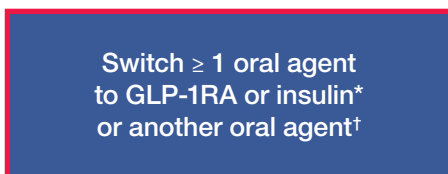


If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

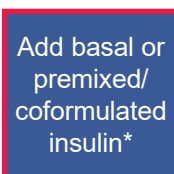
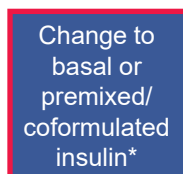
THEN

If on triple oral therapy



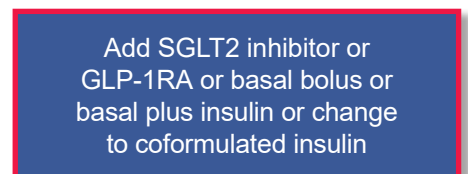
OR

If on GLP-1RA



OR

If on basal insulin*



PBS = Pharmaceutical Benefits Scheme, SU=sulfonylurea, TZD= thiazolidinedione, DPP-4 = dipeptidyl peptidase-4, GLP-1RA= glucagon like peptide 1 receptor agonist, SGLT2 = sodium glucose transporter.
Dark blue boxes indicate usual therapeutic strategy (order is not meant to denote any specific preference); usual refers to commonly available, evidence based, cost effective therapy.
White boxes indicate alternate approaches (order is not meant to denote any specific preference).
Red outlines indicate the classes of glucose lowering agent that include PBS subsidised products.
 * Unless metformin is contraindicated, or not tolerated, it is often therapeutically useful to continue it in combination with insulin.
 † Switching an oral agent is likely to have the smallest impact on glycaemia.

AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

Table of Evidence and Properties of Glucose-Lowering Agents†

Glucose-lowering Class and Drugs	Mechanism of Action	Outcome data	Contraindications	Precautions, Side Effects and Administration	Cost and Accessibility
Biguanide <ul style="list-style-type: none"> metformin metformin XR 	Reduces hepatic glucose output, lowers fasting glucose levels	UKPDS¹	Renal impairment (eGFR<30 ml/min/m ²) Severe hepatic impairment	Precautions Suspend treatment during acute disease/ conditions with the potential to cause tissue hypoxia or alter renal function. Side Effects GI side effects, lactic acidosis, weight neutral Administration Oral administration Start at low dose and up-titrate Slow release preparations available	General schedule on PBS
Sulfonylureas <ul style="list-style-type: none"> glibenclamide gliclazide gliclazide MR glimepiride glipizide 	Triggers insulin release in a glucose-independent manner	UKPDS² ADVANCE³ - Gliclazide MR	Severe renal or hepatic impairment	Precautions Hypoglycaemia Side Effects Weight gain Administration Oral administration Start at low dose and up-titrate Slow release preparation available	General schedule on PBS
Dipeptidyl peptidase-4 (DPP-4) inhibitors <ul style="list-style-type: none"> alogliptin linagliptin saxagliptin sitagliptin vildagliptin 	Decreases inactivation of glucagon-like peptide (GLP-1) thereby increasing its availability GLP-1 stimulates beta cell insulin release	EXAMINE^{4,5} - Alogliptin SAVOR-TIMI 5^{3,6,7} - Saxagliptin TECOS⁸ Sitagliptin CARMELINA⁹ Linagliptin	Pancreatitis ¹⁰	Precautions Nasopharyngitis-often subsides in 10-14 days Side Effects Rash, pancreatitis, GI disturbances, weight neutral Administration Oral administration Dosage adjustment in renal impairment (except Linagliptin) ¹¹	Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin are PBS subsidised for use with either Metformin or Sulfonylurea (i.e. dual therapy) Linagliptin, Saxagliptin, Sitagliptin and Vildagliptin are PBS subsidised for use with Metformin and Sulfonylurea (i.e. triple therapy). If on any DPP4i plus metformin, addition of dapagliflozin or empagliflozin (i.e. triple therapy) is PBS subsidised Linagliptin, Sitagliptin and Vildagliptin are PBS subsidised for use with insulin
Thiazolidinediones (TZD) <ul style="list-style-type: none"> pioglitazone rosiglitazone 	Transcription factor peroxisome proliferator-activated receptor PPARγ agonists Lowers glucose levels through insulin sensitisation	PROACTIVE¹² - Pioglitazone RECORD¹³ - Rosiglitazone		Precautions Symptomatic heart failure Side Effects Fluid retention, heart failure, increased risk of non-axial fractures in women, increased risk of bladder cancer, weight gain Administration Oral administration	PBS subsidised for use in combination with Metformin or Sulfonylurea or both Patient must have a contraindication or intolerance to Metformin- Sulfonylurea combination PBS subsidised for use with insulin
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)	Precautions Gastrointestinal disorders associated with malabsorption Side effects Bloating and flatulence, weight neutral Administration Oral administration Take with meals as tolerated	General schedule on PBS
Sodium-glucose co-transporter-2 (SGLT2) inhibitors <ul style="list-style-type: none"> canagliflozin dapagliflozin empagliflozin 	Inhibits a Sodium-glucose cotransporter to induce urinary glucose loss and decrease blood glucose levels	EMPA-REG OUTCOME¹⁴ - Empagliflozin CANVAS¹⁵ - Canagliflozin DECLARE¹⁶ - Dapagliflozin	Diminished efficacy with renal impairment (eGFR < 60 ml/min/m ²)	Precautions Avoid use with loop diuretics Side effects Dehydration, dizziness, genitourinary infections (advise adequate fluid intake and meticulous toileting hygiene), ketoacidosis, weight loss Administration Oral administration	Dapagliflozin and Empagliflozin: PBS subsidised for use in combination with Metformin, Sulfonylurea or both PBS subsidised for use with insulin If on dapagliflozin or empagliflozin plus metformin, addition of either saxagliptin or linagliptin (i.e. triple therapy) is PBS subsidised Not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), or glucagon-like peptide-1 Canagliflozin: PBS subsidisation withdrawn
Glucagon-like peptide-1 (GLP-1) receptor agonists <ul style="list-style-type: none"> dulaglutide exenatide exenatide ER liraglutide lixisenatide 	Stimulates beta-cell insulin release and slows gastric emptying	ELIXA^{17,18} - Lixisenatide LEADER¹⁹ - Liraglutide EXSCEL²⁰ - Exenatide	Avoid with history of pancreatitis or pancreatic malignancy	Precautions Dosage adjustment in moderate-severe renal impairment Increased risk of pancreatitis Side effects Nausea, vomiting, weight loss Administration Subcutaneous injection	Exenatide, Exenatide ER and Dulaglutide: PBS subsidised for use in combination with Metformin, Sulfonylurea or both Exenatide (but not Exenatide ER): PBS subsidised for use with insulin Not PBS subsidised for use as monotherapy or in combination with dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a SGLT2 inhibitor
Insulin	Directly activates the insulin receptor	UKPDS² ORIGIN²¹ - Insulin Glargine DEVOTE²² - Insulin degludec		Precautions Consider need for dosage adjustment in moderate-severe renal disease Side effects Hypoglycaemia, weight gain Administration Subcutaneous injection Considered early if BGL is very high	General schedule on PBS Levemir Insulin: PBS subsidisation restricted to Type 1 diabetes

† Gunton JE et al. MJA 2014, 201(11), 650-53.

References:

- UKPDS Group. Lancet 1998;352:854-65.
- UKPDS Group. Lancet 1998;352:837-53.
- ADVANCE Collaborative Group. NEJM 2008;358:2560-72.
- White WB, et al. NEJM 2013;369:1327-35.
- Zannad F, et al. Lancet 2015;385:2067-76.
- Scirica BM, et al. NEJM 2013;369:1317-26.
- Scirica BM, et al. Circulation 2014;130:1579-88.
- Green JB, Bethel MA, et al. NEJM 2015;373:232-42.
- Rosenstock J et al. JAMA 2018; In Press.
- Meier JJ, et al. Diabetologia 2014;57:1320-1324.
- McGill JB, et al. Diabetes Care 2013;36:237-44.
- Dormandy JA, et al. Lancet 2005;366:1279-89.
- Home PD, et al. Lancet 2009, 373:2125-35.
- Zinman B, et al. NEJM 2015;372:2117-28.
- Neal B, et al. NEJM 2017;377:644-657.
- Wiviott SD, et al. NEJM 2018; In Press.
- Pfeff MA, et al. Symposium, 75th Scientific Sessions of the American Diabetes Association; Boston, MA; 2015.
- Bentley-Lewis R, et al. Am Heart J 2015;169:631-38.
- Marso SP, et al. NEJM 2016;375:311-322.
- Holman RR, et al. NEJM 2017;377:1228-1239.
- ORIGIN Trial Investigators, NEJM 2012, 367:319-328.
- Marso et al. NEJM 2017; 377:723-732.