AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM
FOR TYPE 2 DIABETES

Australian Diabetes Society

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

Metformin | SU | DPP-4 inhibitor | SGLT2 inhibitor | Insulin | Acarbose | TZD

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

Sulfonylureas (SU) are the usual initial agent to add to metformin. If SU are contraindicated or not tolerated, another agent may be used.

DPP-4 inhibitor | SGLT2 inhibitor | SU | GLP-1RA | Insulin* | Acarbose | TZD

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- check and review current therapies, stop any that fail to improve glycaemic control
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- review use of therapies
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Third line: Consider triple oral therapy or addition of GLP-1RA or insulin

DPP-4 inhibitor | SGLT2 inhibitor | GLP-1RA | SU | Insulin* | Acarbose | TZD

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THEN

If on triple oral therapy		If on GLP-1RA		If on basal insulin*
Switch ≥ 1 oral agent to GLP-1RA or insulin* or another oral agent†	OR	Change to basal or premixed insulin*	Add basal or premixed insulin*	OR Add SGLT2 inhibitor or GLP-1RA or basal bolus or basal plus insulin or change to premixed 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 in people with Type 2 diabetes.
† Switching an oral agent is likely to have the smallest impact on glycaemia.

diabetes australia

The National Diabetes Services Scheme is an initiative of the Australian Government administered with the assistance of Diabetes Australia.

ndss national diabetes services scheme

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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 • metformin • metformin XR	Reduces hepatic glucose output, lowers fasting glucose levels	**UKPDS**[1]	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 • glibenclamide • gliclazide • gliclazide MR • glimepiride • glipizide	Triggers insulin release in a glucose-independent manner	**UKPDS**[2] **ADVANCE**[3] - 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 • 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 53**[6,7] - Saxagliptin **TECOS**[8] - Sitaglipitn	Pancreatitis[9]	**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)[10]	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). Saxagliptin with dapagliflozin and linagliptin with empagliflozin PBS subsidised for use with metformin (i.e. triple therapy) Linagliptin, Sitagliptin and Vildagliptin are PBS subsidised for use with insulin
Thiazolidinediones (TZD) • pioglitazone • rosiglitazone	Transcription factor peroxisome proliferator-activated receptor PPARγ agonists Lowers glucose levels through insulin sensitisation	**PROACTIVE**[11] - Pioglitazone **RECORD**[12] - 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 • 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 • canagliflozin • dapagliflozin • empagliflozin	Inhibits a Sodium-glucose cotransporter to induce urinary glucose loss and decrease blood glucose levels	**EMPA-REG OUTCOME**[13] - Empagliflozin **CANVAS**[14] - Canagliflozin	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 Dapagliflozin with saxagliptin and empagliflozin with linagliptin PBS subsidised for use with metformin 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 • exenatide • exenatide ER • liraglutide • lixisenatide	Stimulates beta-cell insulin release and slows gastric emptying	**ELIXA**[15,16] - Lixisenatide **LEADER**[17] - Liraglutide	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.	**UKPDS**[2] **ORIGIN**[18] - Insulin Glargine		**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:

1. UKPDS Group. Lancet 1998;352:854-65. **2.** UKPDS Group. Lancet 1998;352:837-53. **3.** ADVANCE Collaborative Group. NEJM 2008;358;2560-72. **4.** White WB, et al. NEJM 2013;369:1327-35. **5.** Zannad F,et al. Lancet 2015;385:2067-76. **6.** Scirica BM, et al. NEJM 2013;369:1317-26. **7.** Scirica BM, et al. Circulation 2014;130:1579-88. **8.** Green JB, Bethel MA, et al. NEJM 2015;373:232-42. **9.** Meier JJ, et al. Diabetologia 2014;57:1320-1324.**10.** McGill JB, et al. Diabetes Care 2013;36:237-44. **11.** Dormandy JA, et al. Lancet 2005;366:1279-89. **12.** Home PD, et al. Lancet 2009, 373:2125-35. **13.** Zinman B, et al. NEJM 2015;372:2117-28. **14.** Neal B, et al. NEJM 2017;377:644-657. **15.** Pfeff MA, et al. Symposium, 75th Scientific Sessions of the American Diabetes Association; Boston, MA; 2015. **16.** Bentley-Lewis R, et al. Am Heart J 2015;169:631-38. **17.** Marso SP, et al. NEJM 2016;375:311-322. **18.** ORIGIN Trial Investigators, NEJM 2012, 367:319-328.