

SECTION 10

Medication

Therapeutic approaches vary for type 1 and type 2 diabetes. In this section we will outline the oral medications which are used in type 2 diabetes and insulin therapy which is used in both type 1 and type 2 diabetes.

It is important to point out that whilst hyperglycaemia is an extremely important part of managing diabetes, other metabolic abnormalities such as dyslipidaemia, hypertension and hypercoagulability are also extremely important in reducing microvascular and macrovascular complications.

The aim of this section is to provide basic information about each of the diabetes medications. We recommend you refer to the MIMS Annual for specific details including interactions between various medications.¹

Oral hypoglycaemic agents

Type 2 diabetes is a progressive disease that is characterised by worsening glycaemia and additional medications are required over time if treatment goals are to be met.² The landmark UKPDS demonstrated that 50% of people with type 2 diabetes will end up on insulin within 7 years.³ However, lifestyle factors such as increasing activity, losing weight and a healthy eating plan remain an important part of self care.

The groups of oral hypoglycaemic agents available are:

- biguanides (metformin)
- sulphonylureas
- meglitinides (glitinides)
- glitazones
- alpha-glucosidase inhibitors
- incretin enhancers and mimetics.

Note: medication will not substitute for healthy eating, weight reduction and / or exercise and the benefits of these need to be reinforced.

There are various treatment algorithms that are being used nationally and internationally. The recently released algorithm from the NHMRC states that ⁴;

- interventions to achieve target HbA1c should begin with lifestyle modification followed by therapeutic options which are selected on the basis of the individual circumstances, side effects and contraindications
- for people with significant hyperglycaemia pharmacotherapy should be commenced in addition to lifestyle modification.

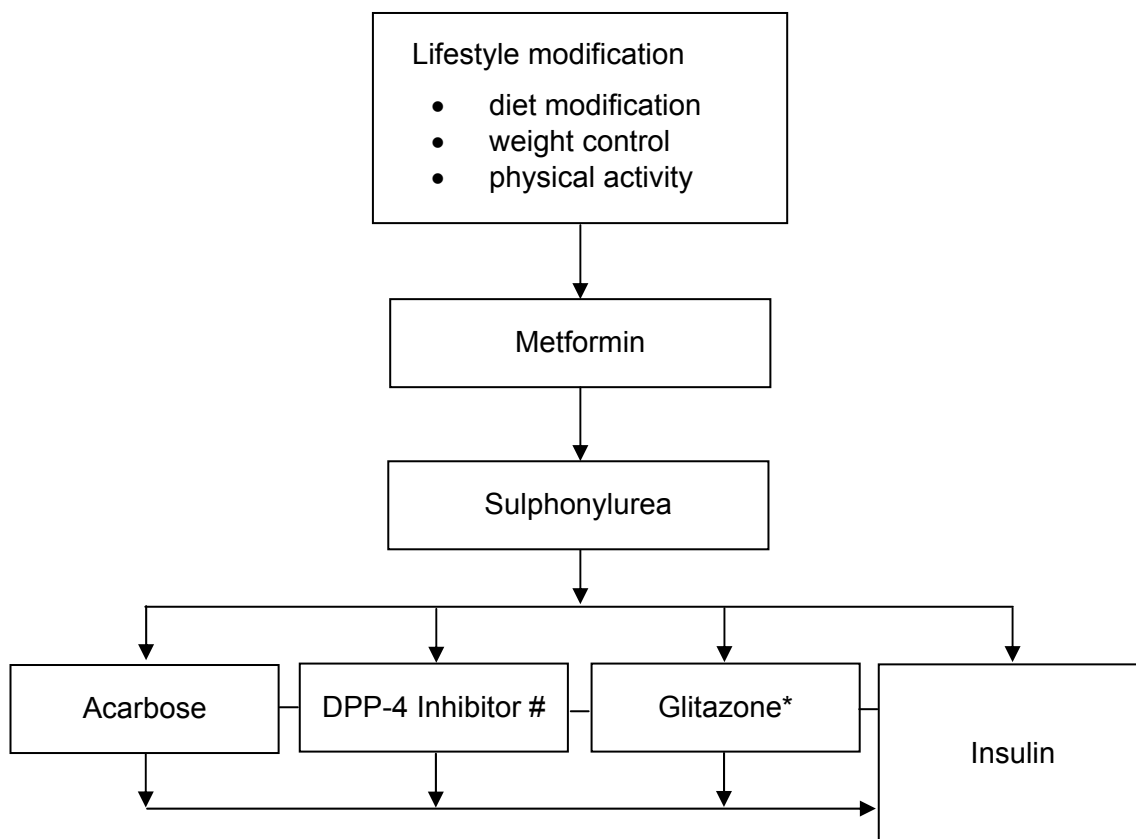
The Australian algorithm includes the following practice points ⁴

- treatment should be intensified if diabetes control is not at target
- it is preferable to add a second oral anti-diabetic medication rather than using a maximum dose of one medication alone
- metformin is contraindicated in people with an eGFR < 30 mL/min/1.73m² and should be used in caution in people with an eGFR of 30-45 mL/min/1.73m²
- people who are not responding to usual diabetes management should be assessed for other conditions (eg Latent Autoimmune diabetes of Adults (LADA), malignancy)

The Australian algorithm is consistent with the UK NICE (2008)⁵ guideline for type 2 diabetes and the IDF guideline (2005)⁶ both of which recommends a trial of lifestyle modification and increased physical activity before considering metformin therapy. While, the recently published consensus statement from America and Europe recognises that supporting the person to make lifestyle improvements is integral they suggest that for most individuals, lifestyle interventions alone fail to achieve or maintain metabolic goals. Their consensus was that metformin should be started at diagnosis alongside lifestyle interventions (unless metformin is contraindicated)²

The NHMRC management algorithm can be seen on page 3 (Figure 1)⁴. The algorithm for commencing and titrating insulin in type 2 diabetes can be found on page 22 of this section. Alternatively the RACGP guidelines have a management algorithm on page 39 ⁷. These can be accessed at www.racgp.org.au/guidelines/diabetes.

Figure 1 Management algorithm for blood glucose control in type 2 diabetes



- The algorithm includes only therapeutic agents available through the PBS.
- If HbA1c >7 consider intensifying treatment provided hypoglycaemia is not a problem.
- # Authorised only as dual therapy with metformin or sulphonylurea where combination metformin and sulphonylurea is contraindicated or not tolerated.
- * Rosiglitazone is not authorised for triple therapy or for use with insulin (from February 1 2009) but is approved only as dual therapy with metformin or sulphonylurea where combination metformin and sulphonylurea is contraindicated or not tolerated.

This algorithm has been adapted from The NHMRC Blood Glucose Control guidelines ⁴

Dosing schedule for oral hypoglycaemic agents⁷

Drug Name	Brand Names	Tablet Size	Daily Dose Range	Approx Duration	Frequency of Admin/day
Biguanides					
Metformin (c,e)	Diabex Diaformin Formet Genrx metformin Glucohexal Glucohexal 1000 Glucomet Glucophage Metforbell Metformin (Genepharm)	Range from 500mg, 850mg, 1g	0.5-3g	12h	2-3
Metformin ER*	Diabex XR Diaformin XR Metex XR Metformin XR	0.5g 0.5g 0.5g 0.5g	0.5-2g	24h	1
Sulphonylureas					
Glibenclamide (b)	Daonil Glimel	5mg 5mg	2.5-20mg	18-24h	1-2
Gliclazide (b)	Diamicron Genrx gliclazide Glyade Mellihexal Nidem	80mg 80mg 80mg 80mg 80mg	40-320mg	18-24h	1-2
Gliclazide ER*	Diamicron MR Oziclide MR	30mg 30mg	30-120mg	24h	1
Glimepiride (b)	Amaryl Aylide Diapride Dimirel Glimepiride Sandoz	1, 2, 3, 4mg	1-4mg daily	>24h	1
Glipizide (b)	Melizide Minidiab	5mg	2.5-40mg	16-24h	1-2
Meglitinides					
Repaglinide (g)	NovoNorm	0.5, 1, 2mg	1.5-16mg	2-3h	1-3
Glitazones					
Pioglitazone (d,e,f)	Actos	15, 30, 45mg	15-45mg	24h	1
Rosiglitazone (d,e,f)	Avandia	4, 8mg	4-8mg	24h	1-2
Alpha-glucosidase inhibitors					
Acarbose (a)	Glucobay	50mg, 100mg	50-600mg in divided doses	3h	1-3
Incretin Enhancers and Mimetics					
Sitagliptin (f,h)	Januvia	100mg	100mg	>24h	1
Exenatide (g)	Byetta	Twice daily non-insulin hypoglycaemic agent. Inject 5mcg bd subcutaneously one hour before two main meals and at least 6 hours apart. After one month increase to 10mcg bd.			
Combination products					
Metformin / Glibenclamide (b,c,e)	Glucovance	250 / 1.25mg 500 / 2.5mg 500 / 5.0mg	Up to 2000/20mg	18-24h	2-3
Metformin / Rosiglitazone (c,d,e,f)	Avandamet	500 / 2mg 500 / 4mg 1000 / 2mg 1000/4mg	Up to 2000/8mg	12-24h	2
Metformin / Sitagliptan (c,e,f,h)	Janumet	500 / 50mg 850 / 50mg 1000 / 50mg	Up to 2000/100mg	>24h	2

*ER = Extended Release

- | | |
|---|---|
| (a) Care renal, gastrointestinal disease. | (e) Care renal, liver and cardiovascular disease. |
| (b) Sulphonylurea | (f) Authority required |
| (c) Metformin | (g) Private script |
| (d) Glitazone | (h) Care, renal insufficiency |

Note: oral agents need to be used with special care in the elderly.

Ensure that patient is aware of the name, dose, dosing time, action and side effects of their medication.

Biguanides

Metformin is a biguanide oral hypoglycaemic agent. It is the only agent available in this class. The major effect of metformin is to decrease hepatic glucose output and lower fasting glycaemia. Typically metformin used on its own will lower HbA1c by approximately 1.5% and does not cause hypoglycaemia.² The most common side effects are gastrointestinal. Metformin therapy is usually weight neutral or can assist with weight loss. This is in contrast to most of the other oral hypoglycaemia agents which tend to be associated with weight gain. The UKPDS also demonstrated a beneficial effect of metformin therapy on cardiovascular outcomes.⁸ It is for these reasons that metformin is usually the first medication started in type 2 diabetes.

Action

- Reduces hepatic glucose production.
- Increases peripheral utilisation of glucose in muscle and fat tissues.
- Decreases intestinal absorption of glucose.
- Decreases insulin requirements for glucose disposal.

Contraindications

- Hypersensitivity to metformin.
- Severe renal impairment (creatinine clearance <30ml/min).
- Ketoacidosis.
- Respiratory failure.
- Severe infection or trauma; substitute with insulin treatment.
- Severe dehydration.
- Alcohol abuse.

Precautions

- Mild to moderate renal impairment – reduce dose.
Consider the following dosages based on creatinine clearance:
 - 60–90mL/minute, 2g/day in divided doses
 - 30–60mL/minute, 1g/day once daily or in divided doses.
- Severe hepatic disease.
- Acute congestive heart failure, recent MI, moderate to severe heart failure.
- Conditions which may be associated with tissue hypoxia eg Gangrene.
- Conditions predisposing to lactic acidosis eg metabolic acidosis.
- The very old (eg >85 years).
- Surgery or patients receiving parenteral iodinated radiograph contrast media (see 'Important Considerations' below).
- Pregnancy.

Side effects

Gastrointestinal side effects are common with metformin and transient. In most patients they are dose related and can be minimised by dose reduction or gradual dose escalation. Metformin should be taken with or after meals to minimise gastrointestinal side effects.

Common

- Gastrointestinal disturbances eg nausea, vomiting, anorexia, abdominal pain, diarrhoea.
- Metallic taste.
- Low vitamin B₁₂ levels.

Infrequent and rare

- Rash.
- Lactic acidosis is a rare but serious adverse effect of metformin. It is fatal in about 50% of cases when it occurs. Symptoms include severe anorexia, nausea, vomiting, abdominal pain, cramps, malaise, unexplained weight loss, slow heart beat, lethargy or sleepiness, dizziness. The risk is higher in some patients with contraindications (see above list) and when metformin is used in higher doses. Patients should notify their doctor immediately if these symptoms occur.

Important considerations

- Metformin may need to be stopped prior to (48 hours) and after surgery or contrast media (iodinated) – depending on renal function and volume of contrast. Always confirm with medical staff or local hospital protocols.⁹
- Metformin should also be used with caution in any severe illness in which tissue oxygenation is potentially reduced (acute respiratory failure, MI, cardiac failure etc).
- Hypoglycaemia is uncommon in patients taking metformin alone, but may occur when it is used in combination with other hypoglycaemic agents or insulin.

Sulphonylureas

Sulphonylurea agents reduce glycaemia by enhancing insulin secretion, with efficacy similar to that of metformin (approximately 1.5% reduction in HbA1c). The major side effects are hypoglycaemia and weight gain.²

Action

- Increase pancreatic insulin secretion.
- May improve insulin sensitivity in peripheral tissue and decrease hepatic glucose output.

Contraindications

- In pregnancy, due to possible teratogenic effects.
- In major surgery, due to possible hypoglycaemic effects.
- Hypersensitivity to sulphonylureas.
- Type 1 diabetes.
- Ketoacidosis.
- Severe renal impairment. (Please consult with GP/MO if concerned).
- Severe hepatic impairment.¹⁰

Precautions

- Mild to moderate renal impairment.
- Elderly people (use agent with lowest risk of hypoglycaemia – see 'Important Considerations' below).
- Severe infection, trauma or other conditions where sulphonylureas are unlikely to control blood glucose; substitute with insulin treatment.

Side effects

Common

- Hypoglycaemia.
- Weight gain.
- Transient visual disturbances eg. Blurred or double vision.

Infrequent and rare

- Gastrointestinal effects eg nausea, diarrhoea, heartburn, anorexia.
- Metallic taste.
- Dermatological reactions eg rash, photosensitivity, exfoliative dermatitis (rare).
- Blood disorders eg thrombocytopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia (rare).
- Hepatotoxicity (rare).

Important considerations

- Ensure that patient is aware of the symptoms of hypoglycaemia so that they can recognise, treat and take measures to prevent it.
- Sulphonylureas should be taken with or immediately before meals to minimise the risk of hypoglycaemia.
- The risk of hypoglycaemia is greatest with glibenclamide, therefore its use should be avoided in the elderly, those with renal and / or hepatic impairment. The risk is lowest with gliclazide and glipizide.
- Exceeding the maximum dose may achieve little benefit. Substitution with, or addition of, another sulphonylurea does not usually improve glucose control.
- Combination therapy with another class of hypoglycaemic agent or insulin may be more appropriate.

Meglitinides

Repaglinide is a member of the meglitinide family of oral hypoglycaemic agents. It is also known as a prandial glucose regulator. It is the only agent available in this class. As this medication is only available on a private script, it is not frequently used.

Action

- Transiently increases pancreatic insulin secretion (similar to sulphonylureas but acts at a different binding site).

Contraindications

- Hypersensitivity to repaglinide.
- Type 1 diabetes.
- Ketoacidosis.
- Children under 12 years.
- Pregnancy and lactation.
- In major surgery, due to possible hypoglycaemic effects.

Precautions

- Impaired renal function.
- Impaired hepatic function.
- Hypoglycaemia.
- Severe infection, trauma or other conditions where meglitinides are unlikely to control blood glucose; substitute with insulin treatment.

Side effects

Common

- Hypoglycaemia.
- Gastrointestinal disturbances eg nausea, abdominal pain, dyspepsia, constipation and diarrhoea.

Infrequent and rare

- Rash.
- Transient visual disturbances eg blurred vision (rare).¹¹
- Increase in liver enzymes.

Important considerations

- Repaglinide has a short duration of action and rapid onset of action. It should therefore be taken immediately before meals.
- The dose of repaglinide should be missed if a meal is skipped. If a meal is added then a dose should be added. It has the principle of 'One meal – one dose, no meal – no dose'.
- Ensure that patient is aware of the symptoms of hypoglycaemia so that they can recognise, treat and take measures to prevent it.

Glitazones

Glitazones or PPAR- γ (peroxisome proliferator receptor activator) agonists increase the risk of oedema and heart failure and current National Prescribing Service guidelines recommend starting insulin as a third agent rather than commencing a glitazone.¹² Insulin has a better long term safety profile. Glitazones double the risk of heart failure. Also, rosiglitazone may increase risk of MI in patients with IHD, therefore it is contraindicated (see contraindications).¹²

Action

- Increase the sensitivity of peripheral tissues to insulin.
- Decrease hepatic glucose output.

Contraindications

- Hypersensitivity to the drug.
- Ketoacidosis.
- Heart failure NYHA Class III and IV.
- Moderate to severe hepatic impairment and where ALT >2.5 times the upper limit of normal.
- Type 1 diabetes.
- Known ischaemic heart disease (IHD)
 - Rosiglitazone is contraindicated in patients IHD, particularly those taking nitrates as it has been shown to increase the risk of myocardial ischaemia.¹³ Pioglitazone does not appear to carry the same risk.

Precautions

- Patients with oedema or mild heart failure, due to risk of fluid retention.
- Anovulatory premenopausal women with insulin resistance as ovulation may resume, therefore consider contraception.

Side effects

Common

- Oedema.
- Weight gain.
- Headache.
- Arthralgia.
- Dizziness.
- Decrease in haemoglobin and haematocrit.
- Increase in total and HDL cholesterol (rosiglitazone).

Infrequent and rare

- Elevated liver enzymes.
- Hepatocellular injury.
- Heart failure.
- Pulmonary oedema.
- Increased risk of peripheral fractures in women.^{7, 10}

Important considerations

- Glitazones can be taken with or without food.
- Hypoglycaemia may occur when it is used with other hypoglycaemic agents or insulin.
- Monitor liver enzymes at the start of the treatment. Stop treatment if ALT rises above 3 times the upper limit of normal or if the patient has jaundice.
- Doses should not be increased before 8 weeks have elapsed; in most trials it has taken between 8 and 18 weeks for full glycaemic response to be seen at any given dose.¹³ Stop treatment if no effect after 6 months.¹⁰
- Advise patients to report signs and symptoms of hepatic dysfunction eg nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine.
- Advise patients to report any weight gain, swollen feet or ankles and breathlessness.
- Ensure that patient is aware of the name, dose, dosing time, action and side effects of their medication.

Alpha–glucosidase inhibitors

Acarbose is an alpha-glucosidase inhibitor. It is the only agent available in this class. Alpha-glucosidase inhibitors are not widely used in Australia largely due to the common side effect of increased flatulence. They are also less effective in reducing HbA1c as compared to metformin and sulphonylureas.

Action

- Inhibits the alpha-glucosidase enzymes in the small intestine, which break down carbohydrates such as starch and sucrose. This action delays the absorption of carbohydrates and thus decreases the sharp, post-prandial rise in blood glucose that occurs after meals.
- Acarbose does not affect the absorption of simple sugars eg glucose and fructose.

Contraindications

- Inflammatory bowel disease.
- Partial intestinal obstruction (or predisposition).
- Gastrointestinal disorders associated with malabsorption.
- Conditions aggravated by formation of intestinal gas eg hernias.
- Severe renal impairment.
- Hypersensitivity to acarbose.
- Pregnancy.
- Patients <18 years.

Precautions

- Ingestion of large amounts of food containing carbohydrate (including sucrose) can lead to gastrointestinal symptoms (flatulence, large amounts of bloating or diarrhoea) during treatment, due to carbohydrate fermentation in the colon. The symptoms are dose dependent and unlikely to be alleviated by taking an antacid.¹⁰ However, they can be reduced by starting patients on low dose and increasing gradually.
- May elevate serum transaminase levels. Decrease dosage if transaminases are elevated and stop treatment if elevations persist.

Side effects

Common

- Gastrointestinal disturbances eg flatulence, abdominal pain and distension, diarrhoea, dyspepsia, nausea.

Infrequent and rare

- Elevation of ALT and AST.
- Hepatitis and / or jaundice.
- Rash and erythema multiforme.
- Anaemia.
- Ileus.
- Oedema.

Important considerations

- Acarbose should be taken directly before meals or with the first few mouthfuls of food or it will not work.
- Hypoglycaemia may occur when it is used with other hypoglycaemic agents or insulin.
- If hypoglycaemia occurs, give glucose but not sucrose because of delayed absorption of sucrose.

Incretin enhancers and mimetics

Glucagon-like peptide-1 (GLP1) and glucose-dependent insulintropic peptide (GIP, formerly known as gastric inhibitory peptide) are naturally occurring incretin hormones produced in the small intestine. GLP-1 and GIP stimulate glucose-dependent insulin secretion from the pancreas. GLP-1 also inhibits glucagon secretion in a glucose dependent manner, and slows gastric emptying which further delays glucose absorption. Incretin enhancers and mimetics reduce the fasting and post prandial glucose⁷ and are similarly effective to the other oral hypoglycaemic agents. These medications are very new and long term safety data is not yet available.

Enhancers (sitagliptin)

Action

Sitagliptan is currently the only agent available in this group. The incretin 'enhancers' are oral medications and slow the breakdown of endogenous GLP-1. They increase glucose-dependent insulin secretion and reduce glucagon production.¹⁰

Contraindications

- Hypersensitivity to sitagliptin.
- Breastfeeding.
- Type 1 diabetes.
- Diabetic ketoacidosis.¹⁴

Precautions

- Renal impairment – consider dosage reduction for creatinine clearance <50 ml/min.¹⁰
- Age <18 – safety and efficacy have not been proven in this group.¹⁴
- Pregnancy.

Side effects

Common

- Upper respiratory tract symptoms.
- Headache.
- Nausea.

Infrequent and rare

- Hypersensitivity reactions e.g. anaphylaxis, angioedema.
- Stevens-Johnson syndrome.⁵

Important considerations

- Not associated with weight gain.
- Do not cause hypoglycaemia unless used with a sulphonylurea or meglitinide.

Mimetics (exenatide)^{10, 15}

Action

Exenatide is currently the only agent available in this group. It is an injected medication (given subcutaneously) which binds to the GLP-1 receptor to enhance insulin secretion and suppress inappropriate glucagon secretion. It also delays gastric emptying, which reduces the rate of glucose absorption, and decreases appetite.

Contraindications

- Hypersensitivity to exenatide.
- Type 1 diabetes.
- Diabetic ketoacidosis.
- Severe gastrointestinal disease eg gastroparesis, dumping syndrome.
- History of pancreatitis with exenatide.
- Severe renal impairment.
- Pregnancy.
- Breastfeeding.

Precautions

- Renal impairment – consider dosage reduction for creatinine clearance <30ml/min.¹⁴
- Age <18 – safety and efficacy have not been proven in this group.

Side effects

Common

- Gastrointestinal disturbances eg nausea and vomiting (occurs in up to 50% of patients but usually improves with continued treatment), diarrhoea, dyspepsia, GORD, abdominal pain.
- Headache, dizziness, feeling jittery.
- Injection site reactions.

Infrequent and rare

- Constipation.
- Taste disturbance.
- Pancreatitis.
- Altered renal function including acute or worsening chronic renal failure.
- Increased serum creatinine concentration.

Important considerations

- Used as an adjunct to metformin and / or a sulphonylurea.
- May aid weight loss in patients with BMI >25.
- Hypoglycaemia is unlikely unless used with a sulphonylurea or meglitinide.
- Less frequent blood glucose monitoring is required with exenatide than with insulin.

Drugs associated with hypoglycaemia

Drugs	Explanatory notes
ACE inhibitors (eg. captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandalopril)	Risk is increased when used with insulin, sulphonylureas or repaglinide. The combination is not contraindicated and commonly used.
Alcohol	Increased risk of hypoglycaemia. When taken with sulphonylureas it may cause disulfiram like reaction. Taking it with metformin can cause or increase the risk of lactic acidosis.
Aspirin (high doses only) and salicylates eg diflunisal, mesalazine, olsalazine, sulphasalazine	High doses of aspirin and salicylates can have hypoglycaemic effects. Low dose aspirin is commonly used in patients with diabetes.
Clonidine	May mask the hypoglycaemic warning symptoms, particularly tachycardia, palpitations and sweating.
Beta blockers (eg atenolol, bisoprolol, carvedilol, metoprolol, pindolol, propranolol, sotalol)	May increase severity and incidence of hypoglycaemia. Also mask some hypoglycaemic warning symptoms. They are not contraindicated in diabetes patients.
NSAIDs (eg diclofenac, ibuprofen, indomethacin, naproxen, ketoprofen, etc)	May cause hypoglycaemia by increasing the amount of sulphonylurea in the blood.
Perhexiline	May cause hypoglycaemia especially in patients taking insulin, sulphonylureas or repaglinide. Monitor blood glucose levels closely. If hypoglycaemia occurs it usually occurs in early treatment.
Quinine, hydroxychloroquine	Quinine may cause hypoglycaemia when used to treat malaria, and possibly leg cramps. Hypoglycaemia may occur with hydroxychloroquine therapy. Monitor blood glucose levels closely.
Quinolone antibiotics (in particular gatifloxacin)	May cause hypoglycaemia especially in combination with hypoglycaemic agents. Monitor blood glucose levels closely.
Selective serotonin reuptake inhibitors (SSRIs)	May decrease the awareness of hypoglycaemic symptoms.
Sulfonamides (eg. sulfamethoxazole, co-trimoxazole ie Septrin, Bactrim)	May cause hypoglycaemia by increasing the amount of sulphonylurea in the blood.

Drugs associated with hyperglycaemia

Drug	Explanatory notes
Antipsychotics	Chlorpromazine is associated with hyperglycaemia especially in doses >100mg daily. Reports of hyperglycaemia and diabetes with atypical antipsychotics (eg olanzapine, clozapine, quetiapine).
Corticosteroids (eg prednisolone, dexamethasone, etc)	Increases risk of hyperglycaemia in people who don't have diabetes, and worsens control in people with diabetes.
Diuretics especially thiazides	Impair diabetes control by raising blood glucose levels especially in high doses. Less likely with low doses.
Glucosamine	Caution in patients with diabetes. May increase blood glucose levels.
Lithium	May cause hyperglycaemia.
Nicotinic acid	May cause hyperglycaemia.
Phenytoin	Hyperglycaemia very occasionally reported; may occur in overdose/long-term high dose treatment.
Quinolone antibiotics (in particular gatifloxacin)	May cause hyperglycaemia. Monitor blood glucose levels closely.
Sugar containing pharmaceuticals eg syrups, elixirs	Patients should be warned of some products that contain significant amounts of sugar.
Sympathomimetics (eg pseudoephedrine, phenylephrine, salbutamol)	Hyperglycaemia has been reported.

Adapted from DATIS Review of Management of Type 2 Diabetes Mellitus in General Practice, updated 2008. This is not an exhaustive list of all the drugs that have been associated with hyperglycaemia. Please refer to MIMS Annual for specific drugs or drug interactions that may predispose to hypoglycaemia or hyperglycaemia.

Insulin

Insulin is a hormone which is secreted by the β cells of the Islets of Langerhans in the pancreas.

It is normally released in response to an increased blood glucose concentration. Many other factors are also involved in its regulation.

Insulin levels increase after a meal and fall as the glucose levels fall to maintain blood glucose levels within a normal range.

Action

- Enhances cellular uptake of glucose.
- Inhibits hepatic glucose production.
- Stimulates glycogen formation and storage in the liver.
- Promotes protein synthesis and storage of fat.

Insulin therapy should therefore aim to mimic these actions and maintain blood glucose levels to as near normal as possible.

Indications

- Type 1 diabetes.
- Type 2 diabetes inadequately controlled with diet, exercise and oral hypoglycaemic agents and in conditions where oral hypoglycaemic agents cannot be used eg pregnancy, surgery, trauma.

Types of insulin

Insulin is derived from:

- Human insulins – molecular structure identical to human insulin and obtained by recombinant DNA technology.
- Insulin analogues – molecular structure similar to human insulin and obtained by recombinant DNA technology.
- Bovine source – purified bovine insulin.

Human insulin is usually absorbed faster than bovine insulin, however it often has a shorter duration.

There are numerous insulin preparations in Australia. The insulins are manufactured by a number of companies, who produce brands that are of similar insulin type and duration of action. For example Actrapid[®] and Humulin R[®] are both short acting or soluble insulins (refer to table on comparative information for insulins).

The type of insulin chosen and the insulin schedule should be based on the individual's needs and lifestyle. The medical officer will discuss the appropriate schedule with the person.

Insulins available

Insulins can be categorised into four groups according to their duration of action.

- **Ultra short acting** – insulin lispro, insulin aspart, and insulin glulisine are soluble, ultra-short acting insulins. They are identical to human insulins except for some molecular structural changes in the insulin chain. As a result, they have more rapid onset of action, which allows them to be given immediately before meals.
- **Short acting** – also called regular, neutral and soluble insulin. This insulin is clear and short acting.
- **Intermediate acting** – cloudy insulin (Isophane). Has prolonged duration of action. The mixed / biphasic insulins also fall into this category. They comprise a combination of ultra-short acting or short acting insulin, in varying proportion, with an intermediate acting insulin.
- **Long acting** – Insulin analogue with a protracted action. It is a clear insulin. It provides a constant basal insulin over 24 hours and is given once daily. Long acting insulin analogues cannot be mixed with other insulins before administration.

Comparative information for insulins⁷

Type	Brand Name	Manufacturer	Nature
Ultra short acting (peak at 1hr, last 3.5-4.5hrs) Insulin lispro Insulin aspart Insulin glulisine	Humalog + Novo Rapid + Apidra +	Lilly Novo Nordisk Sanofi-Aventis	Analogue Analogue Analogue
Short acting (peak at 2-5hrs, last 6-8hrs) Neutral	Actrapid Humulin R Hypurin Neutral	Novo Nordisk Lilly Aspen	Human Human Bovine
Intermediate acting (12-24hrs) Isophane	Humulin NPH Protaphane Hypurin Isophane	Lilly Novo Nordisk Aspen	Human Human Bovine
Long acting Insulin detemir (up to 24 hrs) Insulin glargine (24 hrs)	Levemir Lantus	Novo Nordisk Aventis	Analogue Analogue
Pre-mixed insulins			
Lispro 25% Lispro protamine 75%	Humalog Mix 25 +	Lilly	Analogue
Lispro 50% Lispro protamine 50%	Humalog Mix 50 +	Lilly	Analogue
Insulin aspart 30% Insulin aspart protamine 70%	NovoMix 30 +	Novo Nordisk	Analogue
Neutral 30% Isophane 70%	Humulin 30/70 Mixtard 30/70	Lilly Novo Nordisk	Human Human
Neutral 50% Isophane 50%	Mixtard 50/50	Novo Nordisk	Human

The pharmacokinetics of the different insulins are patient dependent. An empirical approach to dosage together with a 'go slow' policy will result in the smoothest fine tuning of management. Some of these insulins are available as injection devices, pen injectors, disposable insulin pens, cartridges and vials.

+ *Very quick acting. Should be given immediately before eating.*

Insulin initiation and stabilisation in the community

These days most people start insulin without going to hospital. This is better because:

- diabetes can be stabilised around the person's normal day to day routine
- they miss less work or school
- family and personal time is not disrupted.

The person, their doctor and diabetes educator can work together to decide on the best insulin treatment. To assist, ADEA has guidelines to guide practice and standards in this area.¹⁶

The ADEA guidelines for initiating insulin in the ambulatory setting state 'Australian insulin dose changes are authorised in writing by the prescribing medical officer.' Titration of insulin by nurses must only be done if there is an appropriate insulin titration form that has been endorsed by the health service.

Type 2 diabetes

A simple and safe way to initiate insulin is to add bed-time basal (isophane or analogue) insulin to oral antidiabetic agents.

Table 1: Stepwise guide for initiating and adjusting insulin¹⁷

Step 1	<p>ADD 10 units isophane insulin at bedtime.</p> <p>CONTINUE metformin, a sulphonylurea or both (at the same dosage, but no greater than the maximum recommended dose)</p> <ul style="list-style-type: none"> • If evening blood glucose level is high then use 10 units morning isophane insulin. • If both morning and pre-evening meal blood glucose levels are high then consider using twice daily isophane. 												
Step 2	<p>ADJUST Insulin therapy gradually every 3-4 days according to fasting blood glucose (FBG) level until target FBG is reached (usually 4.0-6.0 mmol/L)</p> <table border="1" data-bbox="502 1366 1300 1579"> <thead> <tr> <th>Mean FBG (mmol/L)</th> <th>Adjustment to insulin dose</th> </tr> </thead> <tbody> <tr> <td>> 10</td> <td>Increase by 8 units</td> </tr> <tr> <td>8-10</td> <td>Increase by 6 units</td> </tr> <tr> <td>6-8</td> <td>Increase by 2 units</td> </tr> <tr> <td>4-6</td> <td>No change</td> </tr> <tr> <td>< 4</td> <td>Decrease by 2-4 units</td> </tr> </tbody> </table>	Mean FBG (mmol/L)	Adjustment to insulin dose	> 10	Increase by 8 units	8-10	Increase by 6 units	6-8	Increase by 2 units	4-6	No change	< 4	Decrease by 2-4 units
Mean FBG (mmol/L)	Adjustment to insulin dose												
> 10	Increase by 8 units												
8-10	Increase by 6 units												
6-8	Increase by 2 units												
4-6	No change												
< 4	Decrease by 2-4 units												
Step 3	<p>CHECK overall blood glucose control by measuring HbA_{1c} 3-6 monthly.</p>												
Step 4	<p>If FBG and evening blood glucose are on target but HbA_{1c} is not, look for hidden 'hypers' – blood glucose peaks that occur during the day, often before lunch or after dinner.</p> <p>Options to correct hidden 'hypers' include:</p> <ul style="list-style-type: none"> • changing preceding meal size or composition • increasing activity after meals • adding acarbose • adding a meal-time rapid acting insulin. 												

Continuing oral antidiabetic agents minimises the risk of weight gain and hypoglycaemia.

Type 1 diabetes

Insulin therapy in type 1 diabetes is needed for survival.

The choice of insulin types and regimen has to be guided by a variety of factors, including:¹⁸

- Age of the patient.
- Lifestyle factors.
- Patient and family preferences and management skills.
- Metabolic targets.
- Duration of diabetes.
- Experience of the health care team.
- Affordability and sustainability.
- Associated complications, including hypoglycaemia.

The insulin regimen needs to aim to:

- Provide appropriate basal insulin requirements to cover the needs across 24 hours.
- Provide sufficient insulin levels when needed to cover food intake.
- Have adequate provision for adjustment and correction when needed.
- Minimise blood glucose fluctuation and risk of hypoglycaemia and hyperglycaemia.
- Achieve short-term and long-term metabolic targets.

Most adolescents and adults with type 1 diabetes will be on a four injections per day (basal-bolus) regimen.

With main meals, with intermediate-acting insulin given in the evening or in the morning and evening, or with glargine given once daily (morning or evening).

Insulin pump therapy (continuous subcutaneous insulin infusion – CSII).

The pump contains a ultra short-acting insulin analogue only and is programmed to deliver basal rates to match the person's needs. To cover meals and correct hyperglycaemia, bolus doses are activated by the patient.

Insulin administration in hospital

Insulin can be administered only by injection. Insulin is destroyed if taken orally and therefore is not absorbed if given via this route.

As an inpatient, the registered nurse assigned to care for the person is responsible for:

- checking the medication sheet order (question any discrepancy with the medical officer)
- checking the correct insulin type, dose and time of administration has been documented
- checking blood glucose level prior to administering the insulin
- checking that the injection is given and supervising person's self-administration (if able), people are encouraged to continue to maintain their self-care while in hospital
- supervising and assessing injection technique and site
 - use a new needle each time
 - prime the needle
 - insulin currently in use must **not** be refrigerated
 - mix insulin gently (rock and roll)
 - count to ten after injection before removing the needle
 - rotate injection sites on the abdomen – keep the needle steady
- consulting the diabetes educator if necessary
- people commencing insulin need to be educated about identification, treatment and prevention of hypoglycaemic episodes
- documenting action taken and subsequent progress.

Important points on insulin

The medical officer is responsible for ordering and documenting the insulin dose while the person is in hospital. However, there are some important points about insulin and dosage to bear in mind.

- Insulin type and dosages will vary from person to person. People with type 1 diabetes will have different insulin requirements than those with type 2 diabetes or gestational diabetes. Dosage and effect will vary from time to time for the same person.
- When the person with type 1 diabetes is nauseated or unwell and not eating, as close to usual dose of insulin should be maintained. Food intake needs to be substituted with liquid carbohydrates such as soups, fruit juice or lemonade.
- Some people with type 1 diabetes receiving short acting insulin (eg Actrapid® or Humulin R®) require mid-meal snacks and supper.
- People who receive intermediate / long acting insulin without other insulins, do not generally need snacks unless otherwise indicated.
- When using insulin glargine or detemir it is most important to remember:
 - these insulins are clear and therefore may be confused with the quick acting insulins – mark them clearly as long acting.
 - they cannot be mixed in a syringe with any other insulin.
- If on a twice daily intermediate acting insulin, 2/3 of the dose is usually given in the morning, with 1/3 of the dose before the evening meal.
- If person has P.E.G. feed, please check that the time / action profile of the prescribed insulin coincides with the time-action profile of the feed.
- People who are receiving insulin therapy and are unable to eat, may be able to tolerate oral carbohydrate drinks. If not, please contact the medical officer for review of insulin therapy / IVT.
- Ultra short and short acting insulins are soluble insulins and are the only type that can be given intravenously.
- Long acting insulin analogues cannot be mixed with any other insulin and must be injected separately.
- All preparations are standardised to a single strength (100units/mL) and are suitable for subcutaneous injection.
- When preparing people for surgery see *Hospitalisation* – Section 4.

Important points on administration timing

- Short acting insulins are to be given 20–30 minutes before a meal so that insulin absorption matches the absorption of food. A meal, sufficient carbohydrate intake or IV dextrose must be given within 30 minutes.
- Ultra short acting insulins should be given immediately before or soon after meals.
- Following administration, the insulin action cannot be stopped. The insulin dose must therefore be correct and balanced with the amount of carbohydrate in the meal.
- If the insulin injection is missed or delayed consult the medical officer. Some dose adjustment may be necessary.

Side effects

- Hypoglycaemia.
- Weight gain.
- Local reactions – lipodystrophy, lipoatrophy, erythema, pruritis, allergic reactions.

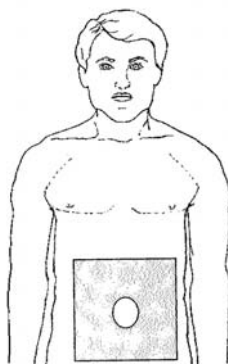
Storage of insulins

- Unopened insulin should be stored in the refrigerator.
- Do **not** freeze insulin.
- Once opened insulin can be stored at room temperature (not exceeding 30°C) for 28 to 30 days (depending on the product) as indicated on the label. Please check product information enclosed with the insulin.
- In hospital, use a one vial or cartridge / one patient policy. Label and date the vial / cartridge when opening them.¹⁹
- Store the insulin you are using out of the fridge and away from direct sunlight.
- Ideally, while in hospital, the person should be encouraged to continue self-care insulin administration. In this case, identify a suitable storage place and store it at room temperature.
- Discard insulin if it is discoloured, has changed in appearance in any way or the expiry date has been reached.
- Insulin is damaged by heat and must not be kept in the car or where the temperature exceeds 30°C.
- If travelling, spare insulin can be kept in a cool bag or vacuum flask.

Important points on injection sites

- Insulin is administered by subcutaneous injection and is absorbed into the capillaries.
- The absorption rate varies with different injection sites. It is most even from the abdomen, intermediate from the buttocks and arm, and slowest from the unexercised thigh.
- The preferred site for subcutaneous injection is the abdomen avoiding a 5cm radius around the umbilicus (see Figure 2 below).

Figure 2



- If the abdomen is unsuitable, for example, in a person who has had abdominal surgery, then the buttocks or thigh can be used.
- Do not use the same spot in the chosen site every time. Move the site around to avoid discomfort and to make sure that the insulin is absorbed evenly. This will also decrease the risk of lipohypertrophy and / or lipoatrophy.
- Assess injection sites and condition of skin. Check for any swelling, hard nodules, indentations, inflammation or pain.
- There is no need to swab the skin with alcohol before injection of insulin.

Insulin variability

The rate of onset, maximum effect and duration of effect will vary between patients. Variables that may influence the actions of insulin include:

- injection site
- local injection site reactions (eg. scars)
- depth of injection
- local massage
- temperature
- exercise
- insulin mixing.

Factors affecting absorption rate

Insulin absorption rate is accelerated by:

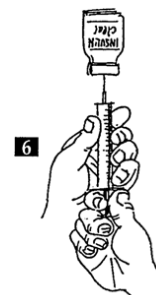
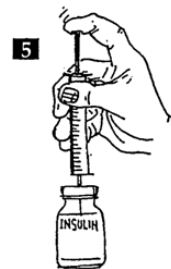
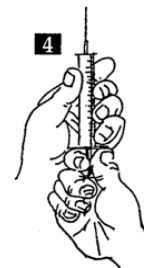
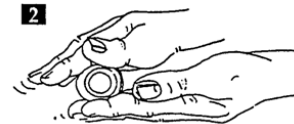
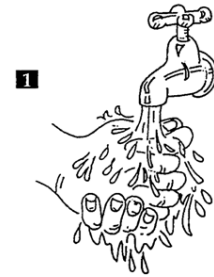
- high temperature such as sauna, hot showers
- massage around the injection site (do not massage following administration)
- depth of injection (should only be given subcutaneously)
- injecting into exercising limbs.

Absorption rate can be delayed by:

- cool temperatures at injection site
- smoking
- lipohypertrophy or scarring at injection site.

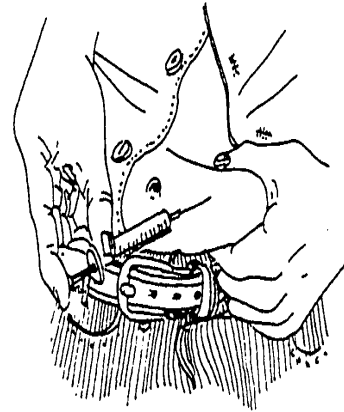
How to draw up insulin (cartridge or vial)

1. Wash and dry hands. Clean the top of the cartridge or vial with an alcohol swab.
2. Gently rotate cartridge / vial to thoroughly mix insulin (do not shake the bottle).
3. Take syringe from packet and remove cap, being careful not to touch the needle top.
4. *Skip 4 & 5 when using cartridges.* Withdraw the plunger to measure the same amount of air equal to the dose required.
5. With the vial upright inject the air into the insulin vial.
6. With the cartridge / vial inverted withdraw the amount of insulin required.
7. Remove the syringe from the cartridge / vial.
8. Tap the syringe barrel to send any air bubbles up.
9. Expel any air bubbles.
10. Check the syringe contains the CORRECT dose.
11. Inject insulin.



Giving the injection

1. Ensure injection site is clean. There is no need to use alcohol swabs on the injection site.
2. "Pinch up" an area of abdomen and gently hold between fingers.
3. Don't squeeze skin tightly.
4. Inject the needle at a 90° angle and inject insulin dose. Count 10 seconds then withdraw the needle. Do NOT massage the area.
5. Dispose of the syringe safely as per hospital policy for 'sharps' disposal.



Rule of Ten's is a simple way to help people on insulin self-inject in a consistent way each time.

Mix insulin before every injection – 10 rocks / 10 rolls

Inject insulin and count 10 seconds before removing the needle.

Giving insulin via an insulin pen device

Insulin pen device or injectors are like large fountain pens with a cartridge of insulin inserted like an ink cartridge (Figure 3). For most people they make insulin injections easier to perform. Many of the insulin pens on the market now are disposed of once the insulin cartridge is empty. It is important that people are educated to use the pen that most suits their needs eg older people with poor vision or poor dexterity often find the Innolet easiest to use (Figure 4 below).

Figure 3

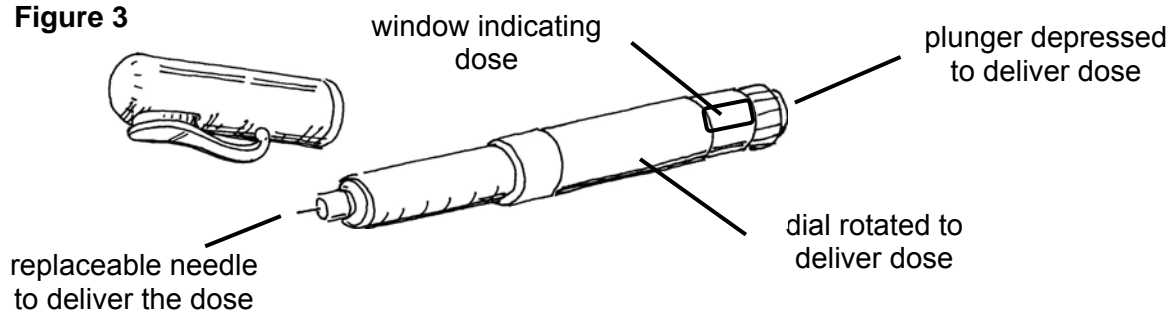
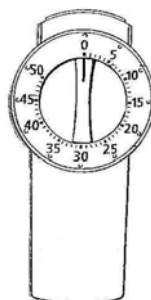


Figure 4



Important points when using an insulin pen device

- Roll the pen between your palms 10 times.
- Move the pen up and down at least 10 times to make sure the insulin is well mixed.
- Put the pen needle on and dial 2 units. Hold the pen with the needle pointing up. Tap the cartridge gently with your finger a few times to make sure any air bubbles collect at the top.
- With the needle still pointing upwards press the button in until the dose selector returns to zero. A drop of insulin should appear at the needle tip. If no insulin appears repeat the air shot.
- Set the required dose by dialling the number of units.
- Inject.

Insulin pens for inpatients

The safest way to administer insulin in a hospital setting is via an insulin syringe.

Nursing staff are not to administer insulin using an insulin delivery device (eg Innolet or pen) with removable pen needles unless the patient is able to self administer independently (ie self inject and then safely dispose of the needle).

If the patient is self administering then it is appropriate for the nurse and patient to check that the dose and time is correct. The nurse then has a supervisory role to ensure correct injection technique and appropriate disposal of sharps.

Note: The Department of Health and Ageing Infection Control guidelines state 'to prevent injury, needles should not be re-sheathed unless an approved recapping device is used'.²⁰

There is no approved re capping device for pen needles (the devices supplied by the pharmaceutical company have not been approved for recapping).

Disposal of syringes

The following advice should be given to people with diabetes regarding disposal of syringes but includes safe disposal of all sharps.

Background²¹

Safe disposal of needles, syringes and lancets is becoming more important with the increased fear of transmission of infectious diseases, and a growing awareness of environmental issues.

Many hospitals and health institutions have formulated their own policies for handling and disposing of sharps. However, no national policies or guidelines exist for community situations.

In reaching its policy statement, Diabetes Australia recognises that there is only one means of safe disposal of needles, syringes and lancets within the community and that is to use an approved, puncture-resistant container. Anything less than this (eg recapping, clipping or using other sub-standard containers) has the potential to cause wounds and infections.

Health professionals involved in diabetes education should act as advocates and promote the necessary skills and education for people with diabetes about the safe disposal of needles, syringes and lancets.

Agreed education message

- Take care at all times.
- Store supplies carefully (eg child-proof cabinet).
- Use a 'standards approved' container.
- Only recap your own needles / lancets.
Recapping your own needle / lancet is a good idea if you are not close to an approved container (eg at a restaurant).
- For local arrangements about the safe disposal of containers, check:
 - your local Diabetes Australia Association.
 - your local council
 - your local public hospital or community health centre.

Supply of syringes

Register with the National Diabetes Services Scheme through Diabetes Australia for syringe supply.

Inform person about the availability of syringes / needles without cost and the fact that they can be mailed out.

Checklist for people on insulin injections

- | | | |
|--------------------------------|---|---|
| Check your insulin | - | type / label / dose / expiry |
| | - | timing |
| | - | sites |
| | - | technique |
| | - | supply and storage |
| | - | syringes and disposal |
| Check your control | - | monitor |
| | - | record results |
| Check your food | - | timing of meals (and snacks if required) |
| Check your exercise | - | if strenuous you will need to adjust insulin / food |
| Check your survival kit | - | to cope with emergencies, keep it handy |
| Check any problem | - | with your doctor or diabetes nurse |

Be aware of resources and contact telephone numbers.

The checklist (Appendix 1) can be used when teaching people to self-administer insulin.

Insulin Pump Therapy

Insulin pump therapy refers to the use of an infusion system for the purpose of delivering a continuous supply of insulin (rapid acting insulin only). The pump is attached via tubing to a small cannula which is inserted subcutaneously into the skin, usually the abdomen.²² In Australia the pump is used for people with type 1 diabetes.

Normally a pancreas secretes a basal amount of insulin over the entire 24 hour period. Although this basal rate varies, there is always insulin present. In addition there is an increase (bolus) in insulin that is secreted automatically in response to food (carbohydrate) intake. Insulin pump therapy aims to mimic the normal physiologic response by providing continuous basal insulin as well as the ability to provide bolus doses whenever there is intake of carbohydrate containing food.

Insulin pump therapy is becoming more widely used both in metropolitan and rural Australia. It is anticipated that this increased utilisation of pump technology will result in more and more patients being admitted to hospital on insulin pump therapy.

When a person is started on an insulin pump they require intensive education and support by a multidisciplinary team including endocrinologist, diabetes educator, dietitian and in some cases a social worker. This team has been trained and is experienced at managing insulin pump therapy. A list of Insulin Pump Centres is available on the Australian Diabetes Educators Association website (www.adea.com.au). If the person lives in a rural or remote area arrangements will need to be made for a shared care arrangement with an Insulin Pump Centre. The diabetes team from the Insulin Pump Centre will ensure appropriate resources and support are available prior to and after commencing the patient on pump therapy. A shared care arrangement helps country diabetes educators to develop and maintain skills in pump education (eg carbohydrate counting, using the pump and managing hypo and hyperglycaemia).

Whilst it may be appropriate for a representative from an insulin pump company to show the person the basics of how the pump operates at **no stage** should they recommend insulin dose adjustments or be providing diabetes education to the patient.²³

Temporary interruption of insulin pump therapy

Insulin pump therapy can be interrupted safely for short periods of time such as showering, sex and sports. Some people may bolus a small amount prior to interrupting whereas others may just disconnect. Usually 60 minutes of interruption can occur in a well person without causing problems.¹

24 hour Help Line advice

Medtronic helpline	1800 777 808
Medical Specialities helpline	(02) 9417 7955
Animas 24 hr Support	1300 851 056
Roche Diagnostics	1800 802 409

What are the advantages of insulin pump therapy?

- Can provide more flexibility in food choices, timing and meal size.
- Hypoglycaemic episodes may be less frequent and less severe.
- Individuals who experience hypoglycaemia unawareness may find that their awareness of hypo begins to return.
- May minimise the dawn phenomenon (high blood glucose levels in the morning)
- May reduce blood glucose fluctuations when diabetes is unstable eg gastroparesis.
- May provide better control and flexibility while travelling, shiftwork, pregnancy and during exercise.²³

Obtaining supplies for insulin pump therapy

The consumables (reservoir, cannula, tubing) are subsidised by the National Diabetes Services Scheme (NDSS). To receive this subsidy each person must be assessed against a criteria which has been endorsed by the Commonwealth Department of Health and Ageing. The assessment may be completed by either a credentialled diabetes educator, endocrinologist or specialist physician.²⁴ At this time only people with type 1 diabetes are eligible for the subsidy.

For information about pump therapy whilst a person is in hospital, please refer to *Hospitalisation* – Section 4.

INSULIN INITIATION CHECKLIST

Patient identification	
UR: _____	OPD: _____
Surname: _____	
Given Names: _____	
D.O.B. _____	Sex: _____
Doctor: _____	Ward: _____

Referred by : _____

Insulin name and dose (please circle) - (as cited letter / phone / GP form / casenotes):

Medications: _____

Device type: _____ Needle size: 5 / 6 / 8 / 12 mm

Signature: _____ Name: _____ Date: _____

LEGEND FOR THE FOLLOWING TABLES (if the section is not applicable then write "NOT APPLICABLE" next to the "DATE")

- L** Low knowledge/skills, unsafe, new diagnosis or has no information. Does not understand basic information and needs reinstruction.
- M** Medium knowledge skills or states demonstrate they may require reinforcements, supervision and explanation. Understands basic information and demonstrates necessary skills for safe self management.
- H** High knowledge/skills safe, able and aware. Assumes responsibility for care and applies knowledge for safe self management.

E Explanation given (detailed)	P Pamphlet given		T Client demonstrated appropriate technique			
	Teaching	Evaluation	Teaching	Evaluation	Teaching	Evaluation
INJECTION TECHNIQUE	DATE:					
Storage of insulin unopened to printed expiry if kept 2 - 8°C (in the fridge). One month expiry after opening, stored in a cool area.						
Information on onset, action and duration of insulin. Timing of injections.						
Hand wash and assemble equipment appropriately. Check all equipment is in order and functioning.						
Check insulin for discolouring, freezing, formation of a white layer, or clumping. Discard if these occur.						
Gentle rotation of the insulin vial or device to ensure uniform suspension of the insulin. 10 rocks and 10 rolls.						
Prime needle. Check the correct dose before injecting. Single use needle. Injection sites rotation and correct depth. Check for lumps or scar tissue. Inject needle at 90°.						
Count 10 seconds, withdraw the needle and let go of the pinched area.						
In case of pen equipment failure, syringe technique is taught.						
Supplies eg. NDSS, chemist. Sharps disposal. Advise single use of syringes/pen needle.						
SPECIFIC INSULIN ISSUES	DATE:					
Cause, signs and symptoms, prevention and treatment of conscious hypoglycaemia.						
Treatment of unconscious hypoglycaemia (glucagon taught to a relative/friend/neighbour/carer).						
Importance of medic alert or similar diabetes identification discussed.						
Individual hypo action plan eg what, who, where, why. Ambulance cover checked.						
Impact of exercise.						
Sick day management.						
Advised to notify Driver Licensing Authority.						
Prevention of hypoglycaemia whilst driving.						
SIGNATURE:						
BLOOD GLUCOSE MONITORING	QA test date:			Competent technique: Yes <input type="checkbox"/> No <input type="checkbox"/>		

References

1. Donohoo E (2009) *MIMs annual* CMPMedica (Australia) Ltd, St Leonards.
2. Nathan D, Buse J B, Davidson M B, Ferrannini E, Holman R R, Sherwin R, and Zinman B (2009) Medical management of hyperglycaemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*, 32(1): p193-203.
3. Wright A, Burden A C F, Paisey R B, Cull C A, and Holman R R (2002) Sulphonylurea inadequacy: Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPCS 57). *Diabetes Care*, 25(2): p330-336.
4. Colagiuri S, Dickinson S, Girgis S, and Colagiuri R (2009) *National evidence based guideline for blood glucose control in type 2 diabetes*. Diabetes Australia and NHMRC, Canberra.
5. The National Collaborating Centre for Chronic Conditions (2008) *Type 2 diabetes : National clinical guideline for management in primary and secondary care (update)*. Royal College of Physicians, London.
6. International Diabetes Federation (2005) *Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes*. International Diabetes Federation Brussels.
7. Harris P, Mann L, London J, Phillips P, and Webster C (2009/10) *Diabetes management in general practice: Guidelines for type 2 diabetes*. Diabetes Australia and Royal Australian College of General Practitioners, Canberra.
8. Holman R, Sanjoy K, Angelyn Bethel A, Matthews D, and Neil H (2008) 10-Year follow-up of intensive glucose control in type 2 diabetes. *The New England Journal of Medicine*, 359(15): p1577-1589.
9. The Royal Australian and New Zealand College of Radiologists (2005) *RANZCR guidelines for metformin hydrochloride and intravascular contrast media*. [Cited 16 September 2009]; Available from: http://www.ranzcr.edu.au/collegroups/reference/EBM/mhicm_guidelines.cfm?
10. Rossi S (2009) *Australian medicines handbook 2009*. Australian Medications Handbook Pty Ltd, Adelaide.
11. Novo Nordisk Pharmaceuticals Pty Ltd. (2009) *NovoNorm® Product Information* [Cited 3 April 2009 (subscription required)]; Available from: www.mimsonline.com.au
12. National Prescribing Service (2008) *Early use of insulin and oral antidiabetic drugs*. National Prescribing Service Newsletter PPS. [Cited December 2008]; Available from: http://www.nps.org.au/health_professionals/publications/prescribing_practice_review/current/early_use_of_insulin_and_oral_antidiabetic_drugs
13. National Prescribing Service (2008) *Rosiglitazone (Avandia) and rosiglitazone with metformin (Avandamet) for type 2 diabetes mellitus*. National Prescribing Service Newsletter RADAR. [Cited 15 September 2009]; Available from: http://www.nps.org.au/health_professionals/publications/nps_radar/current/november_2007/rosiglitazone

14. Lacy C F, Armstrong L L, Goldman M P, and Lance L L (2009) *Drug information handbook: International 18th edition*. Lexi-Comp Inc, Hudson.
15. Endocrinology Drug Sub-Committee (2009) *Therapeutic guidelines: Endocrinology - version 4*. Therapeutic Guidelines Ltd, Melbourne.
16. Australian Diabetes Educators Association (2004) *National standards for the development and quality assessment of services initiating insulin therapy in the ambulatory setting*. Australian Diabetes Educators Association, Canberra.
17. Australian Bureau of Statistics and Australian Institute of Health and Welfare (2008) *The health and welfare of Australia's Aboriginal and Torres Strait Islander peoples*. ABS Catalogue No. 4704.0, AIHW Catalogue No. IHW 21, Commonwealth of Australia, Canberra.
18. Australasian Paediatric Endocrine Group (2005) *Clinical practice guidelines: Type 1 diabetes in children and adolescents*. Department of Health and Ageing, Canberra.
19. The Queen Elizabeth Hospital (2002) *Medication management*. The Queen Elizabeth Hospital, Adelaide.
20. Department of Health and Ageing (2004) *Infection control guidelines for the prevention of transmission of infectious diseases in the health care setting*. Department of Health and Ageing, Canberra.
21. Diabetes Australia (1992) *National policy statement for safe disposal of needles, syringes and lancets*, Diabetes Australia, Canberra.
22. White R (2007) Insulin pump therapy (continuous subcutaneous insulin infusion). *Primary Care Clinics in Office Practice*, 34(4): p845-871.
23. New South Wales Insulin Pump Interest Group (2006) *Insulin pump therapy: An information booklet for diabetes health professionals interested in establishing an insulin pump therapy service*, Diabetes Australia & ADEA, Canberra.
24. Diabetes Australia) *Insulin pump consumables*. [Cited 2009 17 September]; Available from: <http://www.ndss.com.au/Products--Outlets/Insulin-pump-consumables/>