

# How to start oral hypoglycaemic therapy

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[Type 2 diabetes mellitus](#) is common, and will become more so with the expanding Australian waistline. The large government funded Australian Diabetes, Obesity and Lifestyle Study (AusDiab) revealed that there are almost a million people over the age of 25 years with diabetes (1). Even more startling is that almost 1 in 4 Australians over the age of 25 either have diabetes or impaired glucose metabolism (impaired glucose tolerance or impaired fasting glycaemia) (1).

Oral hypoglycaemic agents are the first line therapy for patients diagnosed with type 2 diabetes mellitus if lifestyle modifications are insufficient. One or more of these agents should be commenced (except for those who present with non-ketotic hyperosmolar coma whereby insulin should be used).

In a nutshell (2):

## Asymptomatic hyperglycaemia

- metformin (monotherapy preferred) *or*
- sulfonylurea (monotherapy or with low dose metformin)

## Symptomatic hyperglycaemia and/or obesity

- metformin (monotherapy) *or*
- metformin with sulfonylurea

*See below for details*

Aim for a target of:

**HbA1c < 7.0%**

*and*

**Fasting blood glucose < 6.5 mmol/L**

*Comment: There are many too many oral hypoglycaemic agents to choose from for each to be covered in depth. This article will by large only discuss the medications that I commonly use; i.e., metformin and gliclazide. Both are off patent, inexpensive (to the patient and to the public health system) and of proven effectiveness.*

**Starting metformin**

[Metformin](#) is the most commonly used oral hypoglycaemic agents and it is the first line oral hypoglycaemic agent. It is the only remaining [biguanide](#) on the market. Interestingly enough it is derived from [guanidine](#), found in "French Lilac" or [Galega officinalis](#), a plant used since the Middle Ages for relieving the symptoms of diabetes mellitus (3).

Start with:

### **metformin 500 mg daily or twice daily initially**

Increase dose by **500 mg** every 1-2 weeks according to symptoms and morning fasting blood glucose levels.

Maximum dose: 2.0 - 2.5 g per day

- The dose of metformin should be titrated up every 1-2 weeks. The glycaemic target is a HbA1c of less than 7.0% with an average fasting blood glucose level of 6.5 mmol/L.
- When starting metformin simultaneously with a sulfonylurea, use the "starting" dose of the sulfonylurea and aim to titrate up the dose of metformin first.
- Titrating example:
  - 500 mg daily, *then*
  - 500 mg bd, *then*
  - 500 mg mane and 1 g nocte, *then*
  - 1 g bd, *then*
  - 1 g mane, 500 mg midi, 1 g nocte (or 850 mg tds)

The most common side-effects that tend to limit its use are gastrointestinal; nausea, vomiting and diarrhoea (4). Fortunately, they are usually transient. As such, "start low and go slow" is good advice, especially for the elderly.

Lactic acidosis is a very rare but serious side-effect from metformin. It becomes more common with the degree of renal dysfunction and with age. The estimated number of cases is 0.03 per 1000 patient years (or 1 case per annum in 30,000 patients) with a 50% mortality rate (4).

Trade names for metformin hydrochloride in Australia include: *Chem mart Metformin, Diabex, Diabex XR (slow release), Diaformin, Formet, GenRx Metformin, Geneparm Metformin, Glucohexal, Glucomet, Glucophage, Glucovance (metformin with glibenclamide), Terry White Chemists Metformin*

### **Starting a sulfonylurea**

Sulfonylurea agents have been around for decades. The most commonly used sulfonylureas today are "second generation" agents that are more efficacious and with fewer side-effects. Sulfonylurea drugs should be considered as second-line agents and to be used in conjunction with metformin or as monotherapy if metformin is contraindicated or not tolerated. Sulfonylureas as a class are the most efficient at quickly reducing hyperglycaemia so are particularly useful in those patients with marked symptomatic hyperglycaemia.

As a rule of thumb, most sulfonylurea agents can be started at half a tablet, daily or twice daily though please read the product information.

I recommend:

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## **gliclazide 40 mg daily or twice daily initially**

Increase dose by **40-80 mg** every 2 weeks according to symptoms and morning fasting blood glucose levels.

Maximum dose: 320 mg per day

- The dose of gliclazide should be titrated up every 2 weeks. The glycaemic target is a HbA1c of less than 7.0% with an average fasting blood glucose level of 6.5 mmol/L.
- Doses of up to 160 mg can be given as a single daily dose though divided doses (twice daily) should be used after that.

Sulfonylurea agents are more likely to cause hypoglycaemia compared to metformin so they must be used with care.

Trade names for gliclazide in Australia include: *Chem mart Gliclazide, Diamicron, Diamicron MR (slow release), GenRx Gliclazide, Gyade, Mellihexal, Nidem, Terry White Chemists Gliclazide*

### **About thiazolidinediones (or the "glitazones")**

In Australia, the [thiazolidinediones](#) should be considered to be "third line" agents. They work well but should probably only be used if there is a contraindication or intolerance to either metformin or sulfonylureas, or as an adjunct when maximal therapy has been reached with the other classes. Its disadvantages include (2):

- Expensive;
- a significant period of time is required before maximal hypoglycaemic effect (6-8 weeks);
- contraindicated in heart failure;
- not available on the PBS as monotherapy.

### **About the slow release formulations**

Both metformin and gliclazide come in "slow release" preparations. The advantage to the patient is that these preparations simplify the dosing regimen from divided doses to a single daily dose, and generally also simplify the titrating process.

The disadvantage is that both slow release metformin and slow release gliclazide are proprietary and the cynic would argue that their release is a marketing ploy to recapture the market after the expiration of the original patent. I do not believe that there is any substantial evidence that the once daily formulations are any "better" in terms of endpoints or side-effect profile.

Dose conversion:

**metformin SR 500 mg = metformin 500 mg**

## gliclazide SR 30 mg = gliclazide 80 mg

- metformin SR 500 mg tablet = Diabex XR
- gliclazide SR 30 mg tablet = Diamicron MR

### Reference articles

(1) Dunstan D., Zimmet P., Welborn, T., et al. Diabetes & Associated Disorders in Australia - 2000. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab). [download [PDF](#) :: 884 Kb]

(2) Twigg, S. Individualising initial therapy for hyperglycaemia in type 2 diabetes. *Medicine Today (Update on diabetes)*. September 2005.

(3) Galega officinalis. *Wikipedia*. Last updated: 9 June 2006. [[Link](#)]

(4) Diaformin (metformin hydrochloride). *MIMS Online*. Last updated: 20 January 2006.

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