

## TYPE 2 DIABETES



# PHARMACOTHERAPY OF TYPE 2 DIABETES

2010 UPDATE ON  
"A HEALTHCARE PROFESSIONAL'S  
GUIDE TO TREATMENT"

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**Note to reader:** The contents herein represent the opinions and clinical experience of the author. This booklet is not intended to be a comprehensive text on diabetes management, but rather a user-friendly guide to key management principles for use in the family practice setting. Healthcare professionals must consider the needs of their individual patients and use their clinical judgment when applying the information in this document. Readers who may be interested in more detail and references are referred to the most recent Canadian Diabetes Association clinical practice guidelines. In addition, physicians should consult the most recent version of the *Compendium of Pharmaceuticals and Specialties* for complete prescribing information and product monographs.

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# PHARMACOTHERAPY

## GLYCEMIC TARGETS

The 2003 Canadian Diabetes Association's Clinical Practice Guidelines [1] recommend the following targets. Therapy in most patients with diabetes should be tailored to achieve an A1C  $\pm$  7.0% in order to reduce the risk of microvascular and macrovascular complications. Lowering glyceimic levels toward the normal range (i.e.  $\pm$  6.0%) should be considered for patients in whom it can be achieved safely.

### TABLE

#### Recommended glyceimic targets [1]

Fasting/preprandial

Normal*	4.0 – 6.0 mmol/L
Target	4.0 – 7.0 mmol/L

2 hours postprandial

Normal*	5.0 – 8.0 mmol/L
Target	5.0 – 10.0 mmol/L

A1C

Normal*	$\pm$ 6.0%
Target	$\pm$ 7.0%

\* The normal range should be considered if it can be safely achieved.

## CHOOSING A TREATMENT REGIMEN

### Lifestyle

All patients with diabetes should receive healthy lifestyle counselling. While lifestyle remains a cornerstone of diabetes treatment, many patients find it difficult to maintain the necessary changes over the long term. For this reason,

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the CDA guidelines [1] recommend that physicians not rely on lifestyle alone for too long.

- A weight loss goal of 5 to 10% of initial body weight for obese patients with type 2 diabetes is recommended to improve glycemic and metabolic control.
- People with diabetes should follow Canada's Guidelines for Healthy Eating.
- Patients should be encouraged to accumulate at least 150 minutes of moderate-intensity aerobic exercise each week, spread over at least 3 days of the week or, if willing, 4 hours or more of exercise per week.
- Patients should be encouraged to perform resistance exercise 3 times per week.
- An exercise ECG stress test should be considered for previously sedentary individuals with risk factors for CVD who wish to undertake exercise more vigorous than brisk walking.
- Continue to encourage and support smoking cessation.

## Pharmacotherapy

If glycemic targets have not been met within 2 to 3 months on lifestyle management alone, antihyperglycemic agents (oral agents and/or insulin) should be initiated. If marked hyperglycemia (i.e. A1C  $\geq$  9.0%) is present at diagnosis, pharmacotherapy should be initiated immediately (concomitant with lifestyle counselling).

Most oral agents have the potential to lower A1C by about 1.0 to 1.5% (acarbose [Prandase], nateglinide [Starlix], and orlistat [Xenical] lower A1C by about 0.5%). DPP-4 agents lower A1c by about 0.7% and GLP-1 analogues & mimetics by 0.8-1.2%. Thus, if initial A1C is  $\geq$  9.0%, initial combination therapy should be considered targeting insulin resistance and insulin sensitivity.

The UKPDS demonstrated that 2, if not 3, different agents in combination will frequently be required [15]. If glycemic targets are not met on monotherapy, agent(s) from another class should be added. Adding a drug from another class of agents often addresses the progressive nature of hyperglycemia. The initial use of combinations of submaximal doses, compared to monotherapy at

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the maximum dose, results in more rapid and better glucose control without a significant increase in side effects. Oral agents of one class may be combined with agents of another class and/or insulin. Combined formulations are available for rosiglitazone + metformin (Avandamet), and rosiglitazone + glimepiride (Avandaryl).

Do not combine drugs in the same class, such as a sulphonylurea with a meglitinide. Where metabolic decompensation is present, initial use of insulin should be considered (see Insulin, p. Insert page No).

There are many factors to consider when choosing a pharmacologic treatment regimen, including:

- Level of glycemia and presence of symptoms of diabetes
- Age of the patient
- Predominance of insulin resistance or insulin deficiency
- Renal and hepatic function
- Cardiovascular disease
- Concomitant pharmacotherapy for other health conditions
- Motivation to reach target levels
- Psychosocial deficits that may impact medication administration or safety
- Ability to pay
- Side effects of medications (e.g. risk of hypoglycemia or GI distress)
- Possible multiple beneficial effects of certain medications

## MANAGEMENT OF HYPERGLYCEMIA

The following algorithm summarizes the guideline-recommended approach to the management of hyperglycemia in type 2 diabetes.

### Lifestyle

Initiate lifestyle modifications. Although lifestyle modifications have overall health benefits, they are often not sufficient to lower blood glucose to target. Therefore, do not rely on lifestyle measures alone for more than 2 or 3 months. If A1C >9.0%, start pharmacologic therapy together with lifestyle.

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## PHARMACOTHERAPY IN ADDITION TO LIFESTYLE

Initiate pharmacotherapy with Metformin. Generally Metformin is safe, cost effective, does not promote weight gain and the UKPDS suggested that Metformin may confer some cardiovascular benefits. Metformin is available from many generic manufacturers in 500 mg or 850 mg tabs as well as in extended action form (Glumetza) 500 or 1000 mg. The usual dose is 2000 mg/day but because of the potential side effect of GI irritation, one should start with a low dose such as 250 mg once a day and titrate up to the maximal tolerated or therapeutic dose over a period of 2-3 weeks.

If A1C >9.0%:

1) Initiate combination therapy with 2 agents from different classes (see above). If patient does not achieve target, add another oral agent (i.e. a third agent) from another class or add insulin.

OR

2) Initiate basal and/or preprandial insulin. If patient does not achieve target, intensify the insulin regimen or add an oral agent (in this order): metformin, secretagogue, TZD, acarbose. (See precautions re: use of TZD plus insulin).

The lag period between adding antihyperglycemic agents should be kept to minimum, with consideration given to the pharmacokinetics of the agents used. Metformin and sulphonylureas reach maximum effect very rapidly, but the TZDs (glitazones) may take several months to show maximal effect. We should aim to achieve glycemic control (A1c <7%) within 6-12 months.

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## Mechanism of Action of Oral Antihyperglycemic Medications

**Biguanides (i.e., metformin).** Metformin works by directly inhibiting hepatic glucose production. In addition, metformin slightly increases sensitivity to insulin by reducing hyperglycemia.

**Thiazolidinediones (e.g., pioglitazone, rosiglitazone).** Through the activation of the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR-g), these agents diminish insulin resistance, especially in the muscles and adipose tissue, and, at higher doses, in the liver.

**Alpha-glucosidase inhibitors (i.e., acarbose)** work in the intestines, where they competitively inhibit the enzymes responsible for the conversion of complex sugars into simple sugars.

**Sulfonylureas (e.g., gliclazide, glyburide)** work by stimulating insulin secretion through the modulation of potassium channels in pancreatic beta-cells.

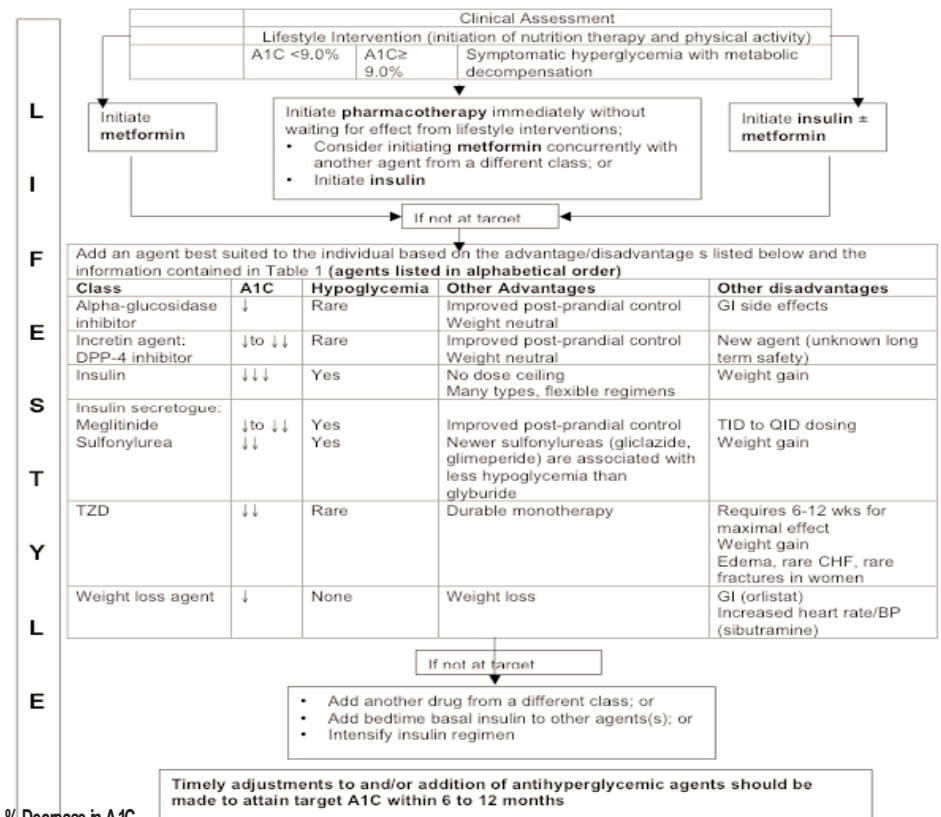
**Non-sulfonylurea insulin secretagogues (e.g., nateglinide, repaglinide)** are similar to sulfonylureas in mechanism of action: the blockade of pancreatic potassium channels. However, compared to sulfonylureas, these have a more brief and immediate effect.

**GLP-1 derivatives (e.g., exenatide, liraglutide).** The incretin effect describes the difference in insulin secretion observed when people are administered glucose orally versus by infusion. The difference in the incretin effect between normal controls and patients with type 2 diabetes is attributed to an impaired action of gut hormones (incretins), such as GLP-1 and GIP. These agents mimic the actions of endogenous GLP-1 to address the imbalance.

**DPP4 inhibitors (e.g., sitagliptin, vildagliptin).** These agents work by inhibiting the enzyme DPP4, which is responsible for inactivating both GLP-1 and GIP.

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## Management of Hyperglycemia in Type 2 Diabetes



% Decrease in A1C

↓ = <1%

↓↓ = 1-2%

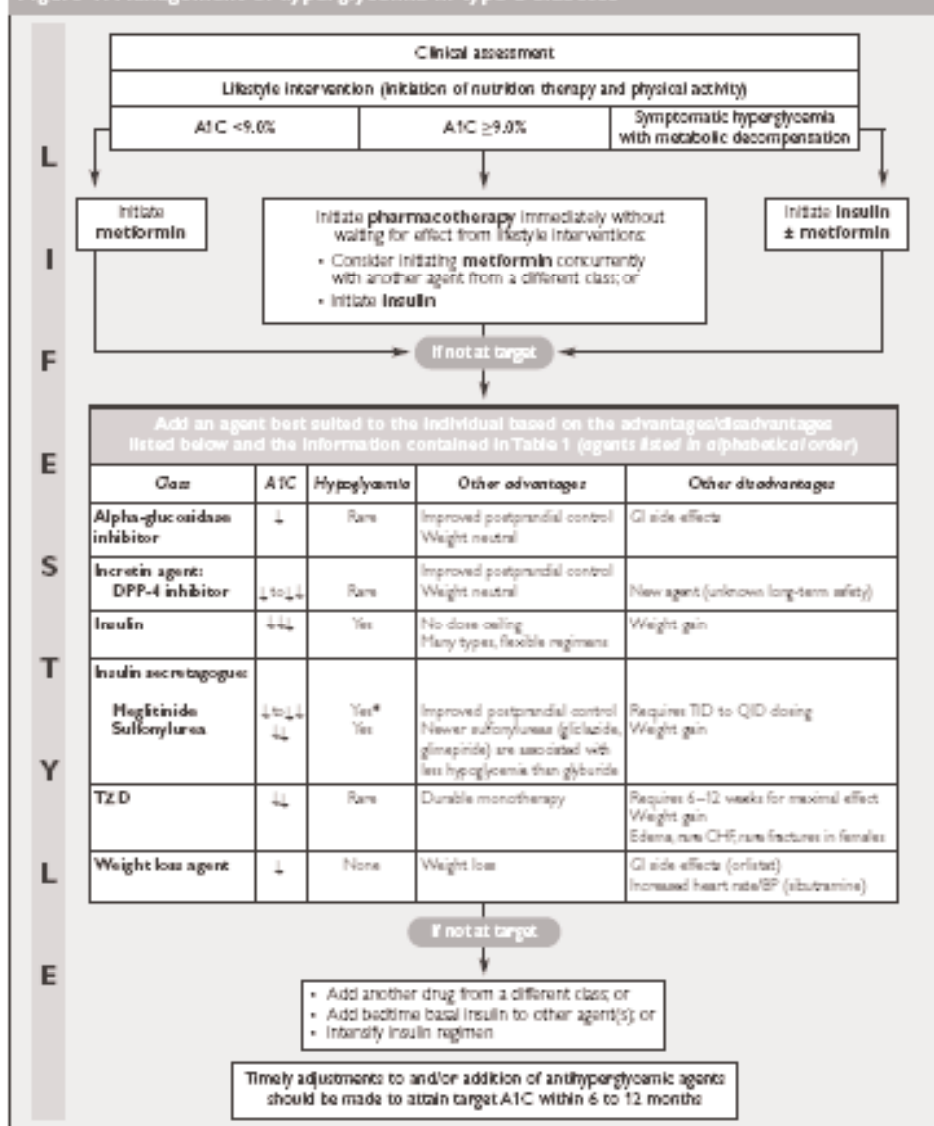
↓↓↓ = >2%

CDA Clinical Practice Guidelines Expert Committee

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Figure 1. Management of hyperglycemia in type 2 diabetes



A1C = glycated hemoglobin  
BP = blood pressure  
CHF = congestive heart failure

DPP-4 = dipeptidyl peptidase-4  
GI = gastrointestinal  
TZD = thiazolidinedione

↓ = <math>< 1.0\%</math> decrease in A1C  
↓↓ = 1.0–2.0% decrease in A1C  
↓↓↓ = >math>> 2.0\%</math> decrease in A1C

**Note:** Physicians should refer to the most recent edition of the Compendium of Pharmaceuticals and Specialties (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information

\*Less hypoglycemia in the context of missed meals

## TREATMENT - ORAL AGENTS

### **BIGUANIDES:**

Act mainly by reducing hepatic glucose production. Indicated in the presence of fasting hyperglycemia. Exerts some effect on skeletal muscle by enhancing glucose uptake (though the mechanism of this action is not well known) and increasing insulin sensitivity. Can cause gastric discomfort and diarrhea, and has been associated with lactic acidosis in the presence of renal or hepatic dysfunction. Taken with meals (usually with breakfast & supper) in order to decrease gastric irritation. Not associated with weight gain and works particularly well with a TZD or an incretin therapy. Does not cause hypoglycemia. May be used with insulin.

### **Metformin (Glucophage)**

Tablets: 500 mg and 850 mg

Starting dose: 1/2 a 500-mg tablet daily

Titration/dosing: Titrate to a maximum dose of 2.5 g/day.

Very little additional benefit at doses > 1500 mg/day, doses greater than 2000 mg/day are less effective and the maximal therapeutic dose is usually 2000 mg/day.

### **Slow-release metformin (Glumetza)**

Tablets: 500 mg and 1000 mg.

Starting dose: 1000 mg OD

Titration/dosing: Titrate to a maximum dose of 2 g OD

(4 x 500 mg QD). Recommended once daily with the evening meal.

Very little additional benefit at doses > 2000 mg/day.

### **Thiazolidinediones (TZDs or glitazones)**

Increase insulin sensitivity and decrease hepatic glucose production. TZD monotherapy is not currently indicated in the symptomatic patient in Canada; rather, a combination with metformin or a secretagogue or insulin to reduce glucose toxicity may be needed initially until therapeutic levels of TZD are reached. Importantly, full effectiveness of TZDs may not be achieved for up to

## TREATMENT - ORAL AGENTS

12 weeks. It is important to encourage adherence to therapy regardless of early lack of observable benefit. Utilizing endogenous insulin, the patient using a TZD will not experience hypoglycemia. These drugs may induce mild edema or fluid retention, which may be reduced with diuretics. Do not use in patients with CHF (NYHA Class III or IV). Discontinue immediately if CHF develops. When used in combination with insulin (not currently an approved indication in Canada), may increase the risk of edema or CHF. Not recommended in patients with active liver disease. Only if symptoms warrant should follow-up liver function tests be performed.

Preservation of pancreatic beta cell function is a feature of TZD treatment and in the DREAM trial (NEJM 2006), rosiglitazone decreased the progression of pre-diabetes to diabetes. The ADOPT study showed rosiglitazone had the longest period of time before monotherapy failure and the PROACTIVE trial showed prolongation of the time to insulin requirement with pioglitazone.

A meta-analysis by Nissen in 2006, suggested that rosiglitazone may increase risk of myocardial infarction but subsequent studies including RECORD, ACCORD, VADT and BARI-2D have not shown signs of increased heart risk.

### **Rosiglitazone (Avandia)**

Tablets: 2 mg, 4 mg, 8 mg

Starting dose: Usual starting dose 4 mg OD

Titration/dosing: 8 mg in 3 months if glycemic goals have not been reached.

Dosage range is 2 mg to 8 mg/day; 4 mg BID is most effective.

### **Pioglitazone (Actos) and generics**

Tablets: 15 mg, 30 mg, 45 mg

Starting dose: Usual starting dose 30 mg

Titration/dosing: Increase to 45 mg in 3 months if needed. Dosage range is 15 to 45 mg.

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## INCRETIN THERAPIES

Incretins are small peptide hormones that are secreted by the gut in response to ingestion of food. The hormones glucose dependant insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). The incretin hormone that is most involved in glucose regulation is GLP-1 which is secreted by the L cells in the terminal ileum. It is known as an incretin hormone because it acts to augment glucose dependant insulin secretion by the pancreatic beta cell. The "incretin effect" may augment insulin production by up to 60% but it does so in a glucose dependant manner so that the higher the glucose level, the greater the increase in insulin production. This protects against hypoglycemia by titrating insulin production to need. GLP-1 also decreases glucagon secretion by the alpha cells of the pancreas, thereby decreasing glucose production by the liver. There are also central effects of GLP-1 in stimulating the satiety centre in the brain to decrease appetite by signaling increased satiety. There is also a decrease of gastric motility which slows stomach emptying. The effect of GLP-1 is very short because the hormone is broken down and de-activated by the action of the dipeptylpeptidase enzyme (DPP-4).

EFFECTS OF GLP-1 HORMONE in glucose regulation

1. Increases glucose dependant insulin secretion
2. Slows gastric emptying
3. Inhibits glucagon secretion; thereby decreasing glucose production
4. Increases satiety, decreases appetite

Rationale: GLP-1 levels are decreased in people with diabetes and may be a contributory factor to obesity & post prandial hyperglycemia. Increasing GLP-1 levels may restore glucose homeostasis. In order to increase GLP-1 levels we can either administer a synthetic GLP-1 analogue which is not broken down by DPP-4 or augment natural GLP-1 levels by inhibiting the DPP-4 enzyme.

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### DPP-4 Inhibitors

Oral medications which inhibit the action of DPP-4.

Increase levels of GLP-1, thereby increasing post prandial insulin secretion in a glucose dependant manner by up to 60%.

Decrease Glucagon secretion by the alpha cells of the pancreas, thereby decreasing new glucose formation by the liver.

The effects of slowed gastric emptying and the central effect of increased satiety are minimally affected by DPP-4 inhibitors but there may be modest weight loss or at least no weight gain. The expected A1c reduction is about 0.7%.

These agents are generally approved for addition to Metformin and in combination with Metformin we expect a 1.5-2% A1c reduction with no risk of hypoglycemia and minimal side effects. DPP-4 inhibitors are not approved in pregnancy and should not be used in moderate to severe renal failure eGFR <30 ml/min.

### Sitagliptin (Januvia):

Januvia is marketed by Merck in Canada. It is approved in Canada in combination with Metformin for treatment of Type 2 Diabetes. Tablet size is 100 mg and the usual dose is 100 mg/day.

### GLP-1 Analogues

Injectable synthetic analogues of GLP-1 that have the metabolic action of GLP-1 but are not inactivated by DPP-4.

### Liraglutide (Victoza) (not available in Canada)

A once daily injectable GLP-1 analogue, 97% homologous to human GLP-1, developed by NovoNordisk. The action is prolonged by conjugation to a C-16 fatty acid palmitoyl, which provides resistance to degradation by DPP-4, half life is 13 hours thus allowing once daily injection. Dose is 0.6, 1.2 or 1.8 mg administered by injection with a proprietary disposable pen device. Major side effect is dose dependant nausea that tends to improve over a week or so, weight loss is also a frequent side effect. The starting dose is 0.6 once a day 1.2 mg which may be increased to 1.8 mcg after a week if needed.

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### GLP-1 Mimetics:

Drugs that although chemically distinct to GLP-1 have structural similarities that allow binding to the GLP-1 receptor.

### Exenatide (Byetta) (not available in Canada)

Marketed by Eli Lilly, dose is 5 mcg or 10 mcg. Available in a proprietary disposable pen, separate pens for each dose. Given twice daily. Side effect nausea.

### INSULIN SECRETAGOGUES

Long-acting (sulphonylureas) and short-acting (meglitinides). Act by stimulating the pancreatic beta cell to produce more insulin

### Sulphonylureas

Act mainly by increasing insulin production by closing the K-ATP channel in the beta cell.

### Glyburide (DiaBeta, Euglucon)

Non-selective and increases insulin output regardless of glucose levels, thus it may cause severe and prolonged hypoglycemia, especially in the elderly.

Tablets: 2.5 mg, 5 mg

Starting dose: 2.5 mg OD

Titration/dosing: Maximum dose is 10 mg BID. Dosage range is 1.25 to 20 mg/day. Usual dose is 5 to 10 mg BID. Doses above 15 to 20 mg/day may confer no further benefit.

### Gliclazide (Diamicron, Diamicron MR)

Associated with less hypoglycemia than glyburide, thus more suitable for the elderly. Insulin release is at least partly glucose dependant. Restores first-phase insulin release secretion. No dose adjustment needed in the elderly or those with mild to moderate renal failure (eGFR 15 to 80 mL/min).

## TREATMENT - ORAL AGENTS

### **Gliclazide (Diamicron) & generics**

Tablets: 80 mg

Starting dose: 40 to 80 mg BID

Titration/dosing: Dosage range 40 to 360 mg/day, given in divided dose BID

### **Gliclazide extended release (Diamicron MR) & generics**

Once-daily formulation providing 24-hour glucose control. Each 30-mg MR tablet has the therapeutic equivalency of a regular 80-mg Diamicron tablet.

Tablets: 30 mg

Starting dose: 30 mg OD in the morning

Titration/dosing: Dosage range 30 to 120 mg daily. Titrate to maximum of 120 mg (i.e. 1 – 4 tablets) as 1 dose/day.

### **Glimepiride (Amaryl) & generics**

Once-daily preparation gives 24-hour control. Insulin secretion may be more glucose dependant. Dual elimination by kidney and liver, so may be used in renal failure.

Tablets: 0.5 mg, 1 mg, 2 mg, 4 mg

Starting dose: 1 mg OD

Titration/dosing: Dosage range 0.5 to 8 mg/day

### **MEGLITINIDES (GLUCONORM, STARLIX)**

Very short-acting insulin secretagogues, taken with meals. Cause less hypoglycemia than sulphonylureas as the on/off action is very rapid in the postprandial phase. Useful in those in whom meals are irregular, such as the elderly and shift workers, and in people with predominantly postprandial hyperglycemia. Adherence can be a challenge, requiring reinforcement to encourage the patient to take with every meal.

### **Repaglinide (GlucoNorm)**

Tablets: 0.5 mg, 1 mg, 2 mg

Starting dose: 0.5 mg taken with meals

# MONITORING