

Metformin/glibenclamide (Glucoavance) for type 2 diabetes mellitus

(met-FOR-min, gli-BEN-cla-mide)

Summary

- Metformin combined with a sulfonylurea is a second-line drug treatment for type 2 diabetes mellitus when either drug alone does not improve glycaemic control.
- Metformin/glibenclamide (Glucoavance) 250/1.25 mg, 500/2.5 mg and 500/5 mg fixed-dose combination tablets are not bio-equivalent to the same dose of glibenclamide.
- Glucoavance has not been proven to be more effective than co-administered metformin and glibenclamide. It may be used to improve compliance for patients stabilised on metformin combined with glibenclamide using the standard tablets.
- Glucoavance tablets do not have the dose flexibility of co-administered metformin and glibenclamide standard tablets.
- Glucoavance should be avoided in the elderly and those with renal or hepatic impairment, as glibenclamide increases the risk of severe and prolonged hypoglycaemia in these patients.
- Alert patients to the signs, symptoms and management of hypoglycaemia.

PBS listing

Metformin/glibenclamide (Glucoavance) fixed-dose combination tablets are listed on the PBS as an unrestricted benefit.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing Glucoavance on a cost-minimisation basis compared with identical doses of the individual components, metformin and glibenclamide.¹ Glucoavance is listed as an unrestricted benefit because the PBAC considered that clinicians should determine its place in therapy.

Place in therapy

Metformin/glibenclamide (Glucoavance) fixed-dose combination tablets are a second-line drug treatment for type 2 diabetes mellitus when glycaemic control does not improve with metformin or sulfonylurea monotherapy. As dosing can be inflexible and glibenclamide is not suitable for all patients, Glucoavance is preferred for those already stabilised on both metformin and glibenclamide standard tablets. However, careful dose titration is necessary, as Glucoavance is not bio-equivalent to the same dose of glibenclamide.

A healthy diet and regular exercise are first line for type 2 diabetes

Initiate drug therapy only when diet and exercise do not provide adequate glycaemic control after 3 months, or when hyperglycaemic symptoms are severe or plasma glucose levels are > 20 mmol/L.^{2,3}

Aim for a fasting plasma glucose (FPG) level < 6 mmol/L and glycated haemoglobin (HbA_{1c}) level ≤ 7%.^{2,4} The UK Prospective Diabetes Study (UKPDS) found that a 1% reduction in HbA_{1c} reduced the relative risk of any diabetes-related complication or diabetes-related death by 21%.⁵ Because of progressive loss of pancreatic beta-cell function in type 2 diabetes mellitus⁶⁻⁹ about 50% of patients may not achieve HbA_{1c} ≤ 7% after 3 years of diet, exercise and drug monotherapy, and many will eventually require insulin regardless of when combination therapy is initiated.^{9,10}

Metformin is the drug of first choice for treating type 2 diabetes

Start metformin in patients who are inadequately controlled with diet and exercise.^{2,3,6,7,11} In the UKPDS, metformin reduced the incidence of any diabetes-related complication and all-cause mortality more than diet, sulfonylureas or insulin in overweight patients with newly diagnosed diabetes.^{2,3,6}

Initiate a sulfonylurea when metformin is contra-indicated or not tolerated. Choose shorter-acting sulfonylureas* (gliclazide, glipizide) for the elderly and those with renal or hepatic impairment as the risk of severe and prolonged hypoglycaemia in these patients is increased with longer-acting sulfonylureas† (glibenclamide, glimepiride) (see Safety issues).^{2,3}

* Gliclazide (Diamicon, Glades, Mellihexal, Nidem), glipizide (Melizide, Minidiab)

† Glibenclamide (Daonil, Glimel), glimepiride (Amaryl, Dimirel)

Combination therapy is not a first-line drug treatment when diet and exercise do not improve glycaemic control

Combining metformin with a sulfonylurea is no more effective than either drug alone when initiating drug treatment.¹²⁻¹⁴ Metformin/glibenclamide fixed-dose combination tablets in 16-week and 20-week studies improved mean HbA_{1c} and FPG only slightly more than glibenclamide or metformin alone, and more than 50% of patients achieved HbA_{1c} < 7% with all therapies.^{13,14}

Combine metformin with a sulfonylurea when either drug alone does not improve glycaemic control

Combine metformin with a sulfonylurea when maximal doses of either drug do not achieve FPG < 6 mmol/L and HbA_{1c} ≤ 7%^{2,3,7,11}; substituting a new monotherapy is ineffective.^{3,15}

Initiate combination therapy with metformin and a sulfonylurea by:

- adding metformin to the current sulfonylurea or
- adding a shorter-acting sulfonylurea to metformin in the elderly and those with renal or hepatic impairment; avoid glibenclamide or glimepiride in these patients (see Safety issues).^{2,3}

In the UKPDS, metformin combined with a sulfonylurea decreased mean FPG by 0.47 mmol/L, while continuing sulfonylurea monotherapy led to an increase of 0.44 mmol/L.¹⁰ In another study of patients poorly controlled with diet and glibenclamide alone, adding metformin decreased mean FPG by 3.5 mmol/L and mean HbA_{1c} by 1.7%, while metformin or glibenclamide monotherapy led to a slight decrease of 0.1 mmol/L and 0.4%, and an increase of 0.8 mmol/L and 0.2%, respectively.¹⁵

Metformin/glibenclamide fixed-dose combination tablets are preferred for patients stabilised on co-administered metformin and glibenclamide tablets

Metformin/glibenclamide fixed-dose combination tablets may improve compliance with treatment; however, glibenclamide is not the sulfonylurea of choice in all patients (see Safety issues). The fixed-dose combination tablets do not have dosing flexibility because the tablet strengths (except for the 250/1.25 mg tablets) are fixed for metformin and variable for glibenclamide. Titrating doses of metformin alone frequently changes the dosing regimen which may affect compliance (see Dosing issues).

Metformin/glibenclamide fixed-dose combination tablets are effective when metformin or sulfonylurea monotherapy does not provide glycaemic control.^{16–18} However, they have not been proven to be more effective than co-administered metformin and glibenclamide standard tablets.^{19,20} Retrospective studies using prescription databases have found better compliance with fixed-dose combination tablets.^{19,21} However this was based on the total days' supply of medication divided by the number of days in the study and does not guarantee medication intake.^{19,21}

The effect of targeting postprandial glucose with Glucovance is unclear

Glucovance is not bio-equivalent to standard glibenclamide tablets.^{22,23} There is a range of glibenclamide particle sizes dispersed in Glucovance tablets, which results in two peak plasma concentrations, the first of which targets postprandial glucose.^{22,23} In two studies, mean postprandial glucose excursions (difference between 2 hour-postprandial glucose and FPG) were reduced slightly more than with metformin or glibenclamide monotherapy (0.3–0.7 mmol/L and 0.4–0.9 mmol/L, respectively).^{14,17} It is unclear whether reduction of postprandial glucose independent of HbA_{1c} and FPG improves the microvascular and macrovascular complications of type 2 diabetes mellitus.^{24–26}

Safety issues

Metformin/glibenclamide fixed-dose combination tablets can cause gastrointestinal adverse effects, hypoglycaemia and weight gain.

Metformin/glibenclamide fixed-dose combination tablets have similar adverse effects to those of metformin or glibenclamide monotherapy

In studies, while lower average doses of metformin/glibenclamide as a fixed-dose combination tablet were used compared with either drug alone, the incidence of adverse effects was not greatly reduced.^{13–17} There was a slightly lower or similar incidence of gastrointestinal adverse effects compared with metformin, especially with the higher-strength combination tablets.^{13,14,16}

METFORMIN/GLIBENCLAMIDE FIXED-DOSE COMBINATION TABLETS CAN CAUSE HYPOGLYCAEMIA

Unlike metformin, sulfonylureas frequently cause hypoglycaemia.³ Longer-acting sulfonylureas such as glibenclamide and glimepiride pose a higher risk of severe and prolonged hypoglycaemia than shorter-acting sulfonylureas^{3,27-29}, although a 4-year prospective study found a lower incidence with glimepiride than glibenclamide.²⁹

Hypoglycaemia may occur if metformin and shorter-acting sulfonylureas are switched to metformin/glibenclamide fixed-dose combination tablets. The elderly and those with renal or hepatic impairment are at greatest risk. Hypoglycaemia with sulfonylureas can occur at any dose and the blood glucose thresholds and symptoms vary among individuals.²⁷⁻³⁰ The elderly are particularly susceptible, as their neurological warning signs (e.g. drowsiness, confusion) may be overlooked.^{27,31}

Box 1: Hypoglycaemia: risk factors and common symptoms^{2,3,27,28,31}

| RISK FACTORS FOR HYPOGLYCAEMIA |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none">• Advanced age, renal or hepatic impairment• Loss of pancreatic beta-cell function• Missed meals, increased physical activity• Dehydration, alcohol consumption• Recent hospital admission, multiple medications*• Excessive dosing of antidiabetic drugs |
| COMMON SYMPTOMS OF HYPOGLYCAEMIA |
| Autonomic (adrenaline release) <ul style="list-style-type: none">• Sweating, shaking, palpitations• Hunger, tingling around mouth |
| Neuroglycopenic (central nervous dysfunction) <ul style="list-style-type: none">• Confusion, impaired concentration, lack of coordination• Dizziness, drowsiness, blurred vision• Abnormal behaviour, speech difficulty |
| General malaise <ul style="list-style-type: none">• Headache, nausea |

* Medications that may mask the signs of or potentiate hypoglycaemia include nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, beta blockers, sulfonamides, fluconazole, quinine, oral anticoagulants, fluoxetine and phenytoin^{2,3,32}

Metformin/glibenclamide fixed-dose combination tablets had a slightly higher incidence of hypoglycaemic events than glibenclamide alone, partly due to greater reductions in FPG and HbA_{1c} levels.^{12,14,16} The proportion of patients with FPG level < 2.8–3.3 mmol/L and/or symptoms of hypoglycaemia ranged from 5–18% with metformin/glibenclamide fixed-dose combination tablets, to 2–11% with glibenclamide and 0–2% with metformin.¹³⁻¹⁷

Because of the risk of hypoglycaemia, Glucovance is contraindicated in patients with renal dysfunction (creatinine clearance < 60 mL/min), hepatic insufficiency or alcoholism.³²

SWITCHING METFORMIN TO METFORMIN/GLIBENCLAMIDE FIXED-DOSE COMBINATION TABLETS CAN CAUSE WEIGHT GAIN

The effect of metformin on weight reduction is lost when combined with glibenclamide.^{17,18} Metformin reduces mean weight by 1–3 kg, while metformin/glibenclamide fixed-dose combination tablets or glibenclamide alone increases mean weight by 1–2 kg.^{13,14,16} In a 52-week study, patients taking metformin had a mean weight gain of 3.9 kg after they were switched to metformin/glibenclamide fixed-dose combination tablets.³³

LACTIC ACIDOSIS WITH METFORMIN IS RARE BUT SERIOUS

Lactic acidosis with metformin is rare, with an incidence of 0.03 cases per 1000 patient-years.^{3,32} The risk is increased with high metformin doses, in the elderly, in renal or hepatic impairment, heart failure, alcohol abuse or use of iodinated contrast media.^{3,32}

For more information, refer to the Glucovance product information and the *Australian Medicines Handbook*.

Dosing issues

When switching metformin and glibenclamide standard tablets to the fixed-dose combination, closely monitor blood glucose levels, as the tablets are not bio-equivalent.^{22,23,32}

Do not use the previous doses of metformin and glibenclamide standard tablets to initiate fixed-dose combination therapy. Start with one 500/2.5 mg tablet once or twice a day, taken at the start of a meal.³² Adjust the dose by one tablet every 2 weeks to a maximum of three or four 500/5 mg tablets daily.³² If the combination tablets are to be used in the elderly, start with one 250/1.25 mg tablet once daily and adjust the dose carefully (see Safety issues).³²

Metformin is usually taken two or three times a day and glibenclamide once or twice a day.³ When fixed-dose combination therapy is more than one tablet daily, the tablets should be administered two or three times a day.³² Minimise excessive dosing of glibenclamide in the fixed-dose combination by using the lower-strength tablets (250/1.25 mg or 500/2.5 mg) for dose titration, especially if the combination tablets are to be taken three times a day. In one study, 66% of patients reported symptoms of hypoglycaemia when their dose was increased using the higher-strength tablets (500/5 mg daily).¹⁴

Information for patients

Advise patients that:

- a healthy diet and regular exercise remain important for the management of diabetes
- Glucovance tablets contain two different drugs — metformin and glibenclamide
- metformin/glibenclamide fixed-dose combination tablets may improve compliance and be a cheaper alternative for patients
- metformin/glibenclamide fixed-dose combination tablets can cause hypoglycaemia, gastrointestinal upset and weight gain
- lactic acidosis with metformin is rare
- the risk of hypoglycaemia may be lessened by regular meals containing carbohydrates, drinking plenty of fluids and restricting alcohol intake^{2,32}
- extra tablets are not to be taken when blood glucose levels are high
- the early warning signs and symptoms of hypoglycaemia include sweating, palpitations and confusion, and must be recognised by patients, relatives and/or carers
- glucose or sugar-containing foods (e.g. fruit juice, jelly beans) must be taken immediately when hypoglycaemia occurs and relatives and/or carers must refer patients with impaired consciousness to a hospital.^{2,31}

Suggest or provide the Glucovance consumer medicine information (CMI) when prescribing or supplying metformin/glibenclamide fixed-dose combination tablets.

Revision history

Updated September 2005.

References

1. Australian Department of Health and Ageing. November 2004 PBAC Outcomes — Positive Recommendations. Available at <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-nov04-positive#metf> (accessed 23 December 2004).
2. Therapeutic Guidelines: Endocrinology. Version 3. Melbourne: Therapeutic Guidelines Ltd 2004.
3. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd 2005.
4. Diabetes Australia. Case Detection and Diagnosis – Part 3 December 2001. http://www.diabetesaustralia.com.au/_lib/doc_pdf/NEBG/CD/Part3-CaseDetection-311201.pdf (accessed December 2004).
5. Stratton IM, et al. BMJ 2000;321:405–12.
6. UKPDS Group. Lancet 1998;352:854–65.
7. National Prescribing Centre. MeReC Briefing. Type 2 diabetes (part 1): the management of blood glucose Issue No. 25, August 2004. http://www.npc.co.uk/MeReC_Briefings/2003/briefing_no_25.pdf (accessed December 2004).
8. UKPDS Group. Lancet 1998;352:837–53.
9. Turner RC, et al. JAMA 1999;281:2005–12. et al.
10. UKPDS Group. Diabetes Care 1998;21:87–92.

11. National Institute for Clinical Excellence. Management of type 2 diabetes. Management of blood glucose (Inherited Clinical Guideline G); September 2002. http://www.nice.org.uk/pdf/NICE_INHERITEG_guidelines.pdf (accessed December 2004).
12. Garber A, et al. Diabetes Obes Metab 2003;5:171–9.
13. Garber AJ, et al. J Clin Endocrinol Metab 2003;88:3598–604.
14. Garber AJ, et al. Diabetes Obes Metab 2002;4:201–8.
15. DeFronzo RA, Goodman AM. N Engl J Med 1995;333:541–9.
16. Marre M, et al. Diabet Med 2002;19:673–80.
17. Blonde L, et al. Diabetes Obes Metab 2002;4:368–75.
18. Blonde L, et al. Int J Clin Pract 2004;58:820–6.
19. Blonde L, et al. Diabetes Obes Metab 2003;5:424–31.
20. Duckworth W, et al. J Manag Care Pharm 2003;9:256–62.
21. Melikian C, et al. Clin Ther 2002;24:460–7.
22. Howlett H, et al. Curr Med Res Opin 2003;19:218–25.
23. Donahue SR, et al. Clin Pharmacokinet 2002;41:1301–9.
24. American Diabetes Association. Diabetes Care 2001;24:775–8.
25. The DECODE Study Group. Diabetes Care 2003;26:688–96.
26. Meigs JB, et al. Diabetes Care 2002;25:1845–50.
27. Veitch PC, Clifton-Bligh RJ. Med J Aust 2004;180:84–5.
28. Salas M, Carro JJ. Adv Drug React Toxicol Rev 2002;21:205–17.
29. Holstein A, et al. Diabetes Metab Res Rev 2001;17:467–73.
30. Holstein A, et al. Eur J Clin Pharmacol 2003;59:91–7.
31. McAulay V, et al. Diabet Med 2001;18:690–705.
32. Alphapharm Pty Ltd. Glucovance Product Information. 13 December 2004.
33. Garber AJ, et al. Clin Ther 2002;24:1401–13.

Date prepared: September 2005

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

NPS is an independent, Australian organisation for Quality Use of Medicines, funded by the Australian Government Department of Health and Ageing.

ABN 61 082 034 393 | Level 7/418A Elizabeth Street Surry Hills 2010 | PO Box 1147 Strawberry Hills 2012 | Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | web: www.nps.org.au