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4. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. *Clin Pharmacokinet* 1996; **30:** 94–106.
5. Anonymous. Acarbose for diabetes mellitus. *Med Lett Drugs Ther* 1996; **38:** 9–10.
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7. Hollander P, *et al.* Acarbose in the treatment of type I diabetes. *Diabetes Care* 1997; **20:** 248–53.
8. Buse J, *et al.* The PROTECT study: final results of a large multicenter postmarketing study in patients with type 2 diabetes. *Clin Ther* 1998; **20:** 257–69.
9. Holman RR, *et al.* A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UK Prospective Diabetes Study 44). *Diabetes Care* 1999; **22:** 960–4.
10. Riccardi G, *et al.* Efficacy and safety of acarbose in the treatment of type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study. *Diabet Med* 1999; **16:** 228–32.
11. Chiasson J-L, *et al.* Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359:** 2072–7.

Impaired glucose tolerance. A prospective study of patients with impaired glucose tolerance concluded that acarbose significantly reduced the incidence of cardiovascular disease and hypertension.[1]

1. Chiasson J-L, *et al.* Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290:** 486–94.

Preparations

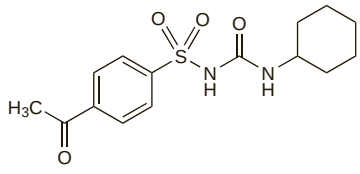
Proprietary Preparations (details are given in Part 3)
Arg.: Glucobay; ***Austral.:*** Glucobay; ***Austria:*** Glucobay; ***Belg.:*** Glucobay; ***Braz.:*** Aglucose; Glucobay; ***Canad.:*** Prandase; ***Chile:*** Glucobay; ***Cz.:*** Glucobay; ***Denm.:*** Glucobay; ***Fr.:*** Glucor; ***Ger.:*** Glucobay; ***Gr.:*** Glucobay; ***Hong Kong:*** Glucobay; ***Hung.:*** Glucobay; ***India:*** Acarbay; Asucrose; Glubose; Glucar; Glucobay; ***Indon.:*** Glucobay; ***Irl.:*** Glucobay; ***Israel:*** Prandase; ***Ital.:*** Glicobase; Glucobay; ***Malaysia:*** Dibose; Glucar; Glucobay; Precose; ***Mex.:*** Glucobay; Incardel; Sincrosa; ***Neth.:*** Glucobay; ***Norw.:*** Glucobay; ***NZ:*** Glucobay; ***Philipp.:*** Glucobay; Gluconase; ***Pol.:*** Glucobay; ***Port.:*** Glucobay; ***Rus.:*** Glucobay (Глюкобай); ***S.Afr.:*** Glucobay; ***Singapore:*** Glucobay; ***Spain:*** Glucobay; Glumida; ***Swed.:*** Glucobay; ***Switz.:*** Glucobay; ***Thai.:*** Glucobay; ***Turk.:*** Glucobay; Glynose; ***UK:*** Glucobay; ***USA:*** Precose; ***Venez.:*** Glucobay.

Acetohexamide *(BAN, USAN, rINN)*

Acetohexamid; Acetohexamida; Acétohexamide; Acetohexamidum; Asetoheksamidi; Compound 33006. 1-(4-Acetylbenzenesulphonyl)-3-cyclohexylurea.

Ацетогексамид

$C_{15}H_{20}N_2O_4S$ = 324.4.
CAS — 968-81-0.
ATC — A10BB31.
ATC Vet — QA10BB31.



Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Acetohexamide). A white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 230 of alcohol and 1 in 210 of chloroform; soluble in pyridine and in dilute solutions of alkali hydroxides.

Profile
Acetohexamide is a sulfonylurea antidiabetic (p.460). Its duration of action is 12 hours or more. It has been given orally in the treatment of type 2 diabetes mellitus (p.431) in a usual initial dose of 250 mg daily before breakfast. The daily dose may then be increased by 250 to 500 mg at intervals of 5 to 7 days, to a maintenance dose of up to 1.5 g daily; increasing the dose above 1.5 g does not usually lead to further benefit. Doses in excess of 1 g daily may be taken in 2 divided doses, before the morning and evening meals.

Preparations
USP 31: Acetohexamide Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Dymelor†.

Biguanide Antidiabetics

Antidiabéticos biguanídicos.

Adverse Effects
Gastrointestinal adverse effects including anorexia, nausea, vomiting, and diarrhoea may occur with biguanides; patients may experience taste disturbance and there may be weight loss. Absorption of various substances including vitamin B_{12} may be impaired. Skin reactions have been reported rarely.

Hypoglycaemia is rare with a biguanide given alone, although it may occur if other contributing factors or drugs are present.

Lactic acidosis, sometimes fatal, has occurred with biguanides, primarily with phenformin. When it has occurred with metformin most cases have been in patients whose condition contra-indicated the use of the drug, particularly those with renal impairment.

Phenformin has been implicated in the controversial reports of excessive cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p.461).

◊ Reviews.

1. Paterson KR, *et al.* Undesired effects of biguanide therapy. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 173–82.
2. Howlett HCS, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Safety* 1999; **20:** 489–503.

Effects on the blood. Megaloblastic anaemia has occurred with biguanide therapy (see Malabsorption, under Effects on the Gastrointestinal Tract, below). A few cases of metformin-induced haemolysis resulting in hyperbilirubinaemia and jaundice have also been described.[1,2]

1. Lin K-D, *et al.* Metformin-induced hemolysis with jaundice. *N Engl J Med* 1998; **339:** 1860–1.
2. Meir A, *et al.* Metformin-induced hemolytic anemia in a patient with glucose-6-phosphate dehydrogenase deficiency. *Diabetes Care* 2003; **26:** 956–7.

Effects on the gastrointestinal tract. ***DIARRHOEA.*** In a retrospective survey,[1] 30 of 265 diabetic patients reported diarrhoea or alternating diarrhoea and constipation, comprising: 11 of 54 taking metformin; 9 of 45 taking metformin with a sulfonylurea; 3 of 53 taking a sulfonylurea only; 5 of 78 on insulin therapy; 2 of 35 on diet alone. Among 150 nondiabetic controls 12 reported diarrhoea. Chronic diarrhoea described as watery, often explosive, and frequently causing faecal incontinence, has been reported as an adverse effect of late onset in patients receiving metformin. Some patients had been on stable metformin therapy for several years before the onset of diarrhoea. Symptoms ceased upon withdrawal of metformin, and recurred in cases of rechallenge.[2,3]

1. Dandona P, *et al.* Diarrhea and metformin in a diabetic clinic. *Diabetes Care* 1983; **6:** 472–4.
2. Raju B, *et al.* Metformin and late gastrointestinal complications. *Am J Med* 2000; **109:** 260–1.
3. Foss MT, Clement KD. Metformin as a cause of late-onset chronic diarrhea. *Pharmacotherapy* 2001; **21:** 1422–4.

MALABSORPTION. Megaloblastic anaemia due to vitamin B_{12} malabsorption in a 58-year-old woman was associated with long-term treatment with metformin.[1]

In a survey of diabetic patients receiving biguanide therapy,[2] malabsorption of vitamin B_{12} was observed in 14 of 46 diabetics taking metformin or phenformin; metformin was more commonly to blame. Withdrawal of the drug resulted in normal absorption in only 7 of the 14. In a series of 10 patients[3] with vitamin B_{12} deficiency associated with metformin, vitamin B_{12} concentrations and blood count abnormalities were reported to have been corrected within 3 months of starting treatment with intramuscular or oral cyanocobalamin; 2 patients were transferred to treatment with other antidiabetic agents.

1. Callaghan TS, *et al.* Megaloblastic anaemia due to vitamin B malabsorption associated with long-term metformin treatment. *BMJ* 1980; **280:** 1214–15.
2. Adams JF, *et al.* Malabsorption of vitamin B and intrinsic factor secretion during biguanide therapy. *Diabetologia* 1983; **24:** 16–18.
3. Andrès E, *et al.* Metformin-associated vitamin B deficiency. *Arch Intern Med* 2002; **162:** 2251–2.

Effects on the liver. Severe cholestatic hepatitis attributed to metformin has been reported.[1]

1. Babich MM, *et al.* Metformin-induced acute hepatitis. *Am J Med* 1998; **104:** 490–2.

Effects on the pancreas. Acute pancreatitis is more commonly associated with phenformin.[1,2] However, there have also been a few cases of pancreatitis associated with metformin, in which renal failure may have precipitated metformin toxicity.[3,4]

1. Wilde H. Pancreatitis and phenformin. *Ann Intern Med* 1972; **77:** 324.
2. Chase HS, Mogan GR. Phenformin-associated pancreatitis. *Ann Intern Med* 1977; **87:** 314–15.
3. Mallick S. Metformin induced acute pancreatitis precipitated by renal failure. *Postgrad Med J* 2004; **80:** 239–40.
4. Fimognari FL, *et al.* Metformin-induced pancreatitis: a possible adverse drug effect during acute renal failure. *Diabetes Care* 2006; **29:** 1183.

Hypersensitivity. Vasculitis and pneumonitis in a 59-year-old woman was associated with use of metformin.[1] Symptoms improved on withdrawal of metformin, but reappeared on its reintroduction. Cutaneous vasculitis in a 33-year-old woman also resolved on withdrawal of metformin and recurred with its reintroduction.[2]

1. Klapholz L, *et al.* Leucocytoclastic vasculitis and pneumonitis induced by metformin. *BMJ* 1986; **293:** 483.
2. Salem CB, *et al.* Rare case of metformin-induced leukocytoclastic vasculitis. *Ann Pharmacother* 2006; **40:** 1685–7.

Hypoglycaemia. UK licensed product information for metformin states that hypoglycaemia does not occur with metformin alone, even in overdosage, although it may occur if given with alcohol or other hypoglycaemics. Interim results from the UK Prospective Diabetes Study,[1] however, indicate that metformin therapy was associated with fewer hypoglycaemic episodes than sulfonylurea or insulin treatment, but more than with diet alone. One or more hypoglycaemic episodes were reported in 6% of the patients receiving the biguanide in this study, although only 1 patient had a severe episode.

1. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for 3 years. *BMJ* 1995; **310:** 83–8.

Lactic acidosis. There is a small but definite risk of lactic acidosis associated with use of biguanide antidiabetics. Most early reports involved phenformin, which was consequently removed from the market in many countries although cases of phenformin-associated lactic acidosis still occur.[1-3] There has therefore been concern about the risks of lactic acidosis with metformin, which is still in wide use. However, lactic acidosis with metformin appears to be much less common: a review suggested that the incidence was of the order of 3 cases per 100 000 patient years, which was 20 times less frequent than with phenformin.[4] This concurs with the findings of the FDA after the introduction of metformin to the US market: in the year after the marketing of metformin in the USA, the FDA had received reports of metformin-associated lactic acidosis in 66 patients,[5] the diagnosis being confirmed in 47. This represented a rate of about 5 cases per 100 000. Most patients who do develop lactic acidosis with metformin have one or more precipitating risk factors such as renal impairment, congestive heart failure, or other conditions predisposing to hypoxaemia or acute renal failure, including septicaemia, acute hepatic decompensation, alcohol abuse, acute myocardial infarction, and shock.[4] A systematic review,[6] which considered results comprising nearly 48 000 patient years of treatment with metformin, concluded that provided metformin was prescribed taking into account the proper contra-indications, there was no evidence of an increased risk of lactic acidosis. Nonetheless, there have been a few reports of lactic acidosis developing in metformin-treated patients without apparent risk factors.[4]

1. Rosand J, *et al.* Fatal phenformin-associated lactic acidosis. *Ann Intern Med* 1997; **127:** 170.
2. Enia G, *et al.* Lactic acidosis induced by phenformin is still a public health problem in Italy. *BMJ* 1997; **315:** 1466–7.
3. Kwong SC, Brubacher J. Phenformin and lactic acidosis: a case report and review. *J Emerg Med* 1998; **16:** 881–6.
4. Chan NN, *et al.* Metformin-associated lactic acidosis: a rare or very rare clinical entity? *Diabet Med* 1999; **16:** 273–81.
5. Misbin RI, *et al.* Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998; **338:** 265–6.
6. Salpeter S, *et al.* Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/05/06).

Treatment of Adverse Effects
Acute poisoning with biguanides may lead to the development of lactic acidosis (see Metabolic Acidosis, p.1667) and calls for intensive supportive therapy. Glucose or glucagon may be required for hypoglycaemia, the general management of which is outlined in Insulin, p.447.

Precautions
Biguanides are inappropriate for patients with diabetic coma and ketoacidosis, or for those with severe infection, trauma, or other severe conditions where the biguanide is unlikely to control the hyperglycaemia; insulin should be used in such situations. Biguanides should not be given to patients with even mild renal impairment, as it may predispose patients to lactic acidosis, and renal function should be monitored throughout therapy. Dehydration may contribute to renal impairment. Conditions associated with hypoxia, such as