4. Levien TL, *et al.* Nateglinide therapy for type 2 diabetes mellitus. *Ann Pharmacother* 2001; **35:** 1426–34.
5. Fonseca V. *et al.* Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improves overall glycemic control. *Diabetes Care* 2003; **26:** 1685–90.
6. Campbell IW. Nateglinide—current and future role in the treatment of patients with type 2 diabetes mellitus. *Int J Clin Pract* 2005; **59:** 1218–28.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nateglin; Starlix; ***Braz.:*** Starlix; ***Canad.:*** Starlix; ***Chile:*** Gluconol; Starlix; ***Cz.:*** Starlix; Trazec; ***Denm.:*** Starlix†; ***Fin.:*** Starlix; ***Ger.:*** Starlix; ***Gr.:*** Starlix; ***Hong Kong:*** Starlix†; ***Hung.:*** Starlix; ***India:*** Glinate; ***Indon.:*** Starlix; ***Irl.:*** Starlix; ***Jpn:*** Starsis; ***Malaysia:*** Starlix; ***Mex.:*** Starlix; ***Neth.:*** Starlix; Trazec; ***Norw.:*** Starlix; ***NZ:*** Starlix†; ***Philipp.:*** Starlix; ***Port.:*** Starlix; Trazec; ***Rus.:*** Starlix (Старликс); ***S.Afr.:*** Starlix; ***Singapore:*** Starlix; ***Spain:*** Starlix; ***Swed.:*** Starlix; ***Switz.:*** Starlix; ***Turk.:*** Starlix; ***UK:*** Starlix; ***USA:*** Starlix; ***Venez.:*** Starlix.

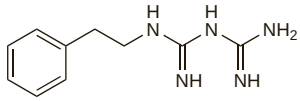
Multi-ingredient: ***Braz.:*** Starform; ***Venez.:*** Starform.

Phenformin Hydrochloride *(BANM, pINNM)*

Fenformina Cloridrato; Hidrocloruro de fenformina; Phenformine, Chlorhydrate de; Phenformini Hydrochloridum. 1-Phenethylbiguanide hydrochloride.

Фенформина Гидрохлорид

$C_{10}H_{15}N_5$,HCl = 241.7.
CAS — 114-86-3 (phenformin); 834-28-6 (phenformin hydrochloride).
ATC — A10BA01.
ATC Vet — QA10BA01.



(phenformin)

Pharmacopoeias. In *Chin.*

Profile
Phenformin hydrochloride is a biguanide antidiabetic (p.437). Although it is generally considered to be associated with an unacceptably high incidence of lactic acidosis, often fatal, it is still available in some countries for the treatment of type 2 diabetes mellitus.

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

Preparations
Proprietary Preparations (details are given in Part 3)
Gr.: Informin; ***India:*** DBI†; ***Port.:*** Debeina†.

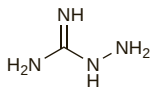
Multi-ingredient: ***Gr.:*** Daopar†; ***India:*** Chlorformin†; ***Ital.:*** Bi-Euglucon†; Bidiabe; Gliben F; Gliformin; Suguan†.

Pimagedine *(rINN)*

Pimagedina; Pimagédine; Pimagedinum. Aminoguanidine.

Пимагедин

CH_6N_4 = 74.09.
CAS — 79-17-4.



Pimagedine Hydrochloride *(USAN, rINNM)*

GER-11; Hidrocloruro de pimagedina; Pimagédine, Chlorhydrate de; Pimagedini Hydrochloridum. Aminoguanidine monohydrochloride.

Пимагедина Гидрохлорид

CH_6N_4,HCl = 110.5.
CAS — 1937-19-5.

Profile
Pimagedine reportedly inhibits the formation of glycosylated proteins (advanced glycosylation end-products) and has other actions including inhibition of aldose reductase. It has been investigated for the prevention of diabetic complications (p.433).

◊ References.

1. Corbett JA, *et al.* Aminoguanidine, a novel inhibitor of nitric oxide formation, prevents diabetic vascular dysfunction. *Diabetes* 1992; **41:** 552–6.
2. Wolffenbuttel BHR, Huijberts MSP. Aminoguanidine, a potential drug for the treatment of diabetic complications. *Neth J Med* 1993; **42:** 205–8.
3. Abdel-Rahman E, Bolton WK. Pimagedine: a novel therapy for diabetic nephropathy. *Expert Opin Invest Drugs* 2002; **11:** 565–74.
4. Thornalley PJ. Use of aminoguanidine (pimagedine) to prevent the formation of advanced glycation endproducts. *Arch Biochem Biophys* 2003; **419:** 31–40.

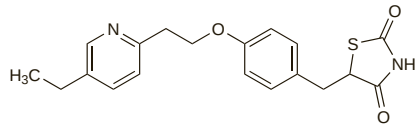
Pioglitazone Hydrochloride

(BANM, USAN, rINNM)

AD-4833 (pioglitazone); Hidrocloruro de pioglitazona; Pioglitazone, Chlorhydrate de; Pioglitazoni Hydrochloridum; U-72107A; U-72107E (pioglitazone). (±)-5-{*p*-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione hydrochloride.

Пиоглитазона Гидрохлорид

$C_{19}H_{20}N_2O_3S$,HCl = 392.9.
CAS — 111025-46-8 (pioglitazone); 112529-15-4 (pioglitazone hydrochloride).
ATC — A10BG03.
ATC Vet — QA10BG03.



(pioglitazone)

Adverse Effects and Precautions
As for Rosiglitazone Maleate, p.458. The effects of pioglitazone on serum lipid concentrations appear to differ from those of rosiglitazone, see below. Other adverse effects reported include upper respiratory-tract infections, haematuria, and visual disturbances. Liver function should be monitored periodically as there have been isolated reports of liver dysfunction, and the drug should be used with caution in patients with hepatic impairment (see below).

An increased incidence of bladder cancer has been seen in *rats* but not in *mice* treated with pioglitazone.

Use is contra-indicated in patients with diabetic ketoacidosis. For precautions and contra-indications to the use of thiazolidinediones in heart failure see Effects on the Heart, under Rosiglitazone Maleate, p.459.

Effects on lipids. Thiazolidinediones are reported to affect serum concentrations of lipids. Compared with placebo,[1,2] pioglitazone has been found to reduce triglycerides, increase high-density lipoprotein (HDL)-cholesterol, and have little or no effect on low-density lipoprotein (LDL)- and total cholesterol. In a study[3] of patients being transferred from troglitazone to either pioglitazone or rosiglitazone, there were decreases in concentrations of triglycerides, LDL- and total cholesterol, and an increase in HDL-cholesterol in those patients on pioglitazone, whereas the opposite occurred for rosiglitazone. Whether these effects of pioglitazone reduce cardiovascular risk in patients with type 2 diabetes is yet to be fully established, but the large prospective PROactive study did suggest that it could reduce the risk of macrovascular events in patients with evidence of macrovascular disease, although the risk of heart failure appears to be *increased* (see Diabetic Complications, below, and Effects on the Heart, under Rosiglitazone Maleate, p.459).

1. Kipnes MS, *et al.* Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med* 2001; **111:** 10–17.
2. Rosenblatt S, *et al.* The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Artery Dis* 2001; **12:** 413–23.
3. Gegick CG, Altheimer MD. Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract* 2001; **7:** 162–9.

Effects on the liver. There have been isolated reports of hepatocellular injury in patients receiving pioglitazone.[1-5]

The UK and US licensed product information recommends that liver enzymes should be checked before starting therapy with pioglitazone; patients with aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given pioglitazone. ALT concentrations should then be monitored periodically during treatment. If ALT concentrations rise to more than 3 times the upper limit of normal and remain so after retesting then treatment with pioglitazone should be stopped; treatment should also be stopped if jaundice develops.

1. Maeda K. Hepatocellular injury in a patient receiving pioglitazone. *Ann Intern Med* 2001; **135:** 306.
2. May LD, *et al.* Mixed hepatocellular-cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; **136:** 449–52.
3. Pinto AG, *et al.* Severe but reversible cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; **137:** 857.
4. Chase MP, Yarze JC. Pioglitazone-associated fulminant hepatic failure. *Am J Gastroenterol* 2002; **97:** 502–3.
5. Farley-Hills E, *et al.* Fatal liver failure associated with pioglitazone. *BMJ* 2004; **329:** 429.

Interactions
When pioglitazone was given with gemfibrozil, an inhibitor of the cytochrome P450 isoenzyme CYP2C8, there was a threefold increase in the area under the concentration-time curve (AUC) of pioglitazone, and a decrease in pioglitazone dose may be needed if it is given with gemfibrozil or similar CYP2C8 inhibitors. Equally, rifampicin, a potent inducer of cytochrome P450, halves the AUC of pioglitazone when both are given, and pioglitazone dose may need to be increased.

Antibacterials. For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving oral hypoglycaemics such as pioglitazone, see p.281.

Pharmacokinetics
Pioglitazone is rapidly absorbed after oral doses. Peak plasma concentrations occur within 2 hours and bioavailability exceeds 80%. Pioglitazone is more than 99% bound to plasma proteins. It is extensively metabolised, primarily by the cytochrome P450 isoenzyme CYP2C8 to both active and inactive metabolites. It is excreted in urine and faeces and has a plasma half-life of up to 7 hours. The active metabolites have a half-life of up to 24 hours.

Uses and Administration
Pioglitazone is a thiazolidinedione oral antidiabetic similar to rosiglitazone (p.458). It is used in the management of type 2 diabetes mellitus (p.431). It is given as pioglitazone hydrochloride but doses are expressed in terms of the base; pioglitazone hydrochloride 1.1 mg is equivalent to about 1 mg of pioglitazone. It is given orally as monotherapy, particularly in patients who are overweight and for whom metformin is contra-indicated or not tolerated. Pioglitazone may also be added to metformin or a sulfonylurea or both, or to insulin, when single-agent therapy is inadequate (but see Administration, below). The usual dose is 15 or 30 mg once daily. This may be increased to a maximum of 45 mg once daily if necessary. Pioglitazone may be taken with or without food.

◊ References.

1. Gillies PS, Dunn CJ. Pioglitazone. *Drugs* 2000; **60:** 333–43.
2. Anonymous. Pioglitazone and rosiglitazone for diabetes. *Drug Ther Bull* 2001; **39:** 65–8.
3. Parulkar AA, *et al.* Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001; **134:** 61–71.
4. O'Moore-Sullivan TM, Prins JB. Thiazolidinediones and type 2 diabetes: new drugs for an old disease. *Med J Aust* 2002; **176:** 381–6. Correction. *ibid.*; **177:** 396.
5. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. *Drugs* 2003; **63:** 1373–1405.
6. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351:** 1106–18.
7. Waugh J, *et al.* Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs* 2006; **66:** 85–109. Correction. *ibid.*; 340–1.
8. Richter B, *et al.* Pioglitazone for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/03/07).

Administration. Although pioglitazone is licensed for use with other antidiabetic drugs, the specifics of licensing and use may vary from country to country. In the UK, use of pioglitazone with insulin was originally considered to be contra-indicated, because of an increased risk of heart failure, although this was subsequently amended to permit dual therapy in patients who could not be given insulin plus metformin. Furthermore, although pioglitazone is licensed for use with metformin or a sulfonylurea (or both if necessary) in patients who do not respond to these drugs, NICE recommends this only in patients unsuited to combination therapy with metformin plus a sulfonylurea.[1] However, in the USA, pioglitazone has always been licensed for use with insulin (with appropriate monitoring), metformin, or a sulfonylurea in any patient in whom single agent therapy is inadequate.

1. NICE. Guidance on the use of glitazones for the treatment of type 2 diabetes (issued August 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA63_Glitazones_Review_Guidance.pdf (accessed 20/08/08)