Adverse Effects and Precautions
As for alpha-glucosidase inhibitors in general (see Acarbose, p.436). Skin rash may occur. Miglitol should be used with caution in patients with renal impairment.

Interactions
As for alpha-glucosidase inhibitors in general (see Acarbose, p.436). Miglitol may reduce the bioavailability of propranolol and ranitidine.

Pharmacokinetics
Miglitol is completely absorbed at a dose of 25 mg, but only 50 to 70% is absorbed at a dose of 100 mg. It is not metabolised, and is excreted unchanged in the urine with a plasma elimination half-life of about 2 hours.

Uses and Administration
Miglitol is an alpha-glucosidase inhibitor similar in action to acarbose (p.436). It is given orally in the management of type 2 diabetes mellitus (p.431), alone or with a sulfonylurea. Usual initial doses are 25 mg three times daily with meals, increased if necessary to a maximum of 100 mg three times daily.

◊ References.

1. Campbell LK, *et al.* Miglitol: assessment of its role in the treatment of patients with diabetes mellitus. *Ann Pharmacother* 2000; **34:** 1291–1301.
2. Scott LJ, Spencer CM. Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. *Drugs* 2000; **59:** 521–49.
3. Standl E, *et al.* Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pract* 2001; **51:** 205–13.
4. Chiasson JL, *et al.* The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care* 2001; **24:** 989–94.
5. Van Gaal L, *et al.* Miglitol combined with metformin improves glycaemic control in type 2 diabetes. *Diabetes Obes Metab* 2001; **3:** 326–31.
6. Drent ML, *et al.* Dose-dependent efficacy of miglitol, an alpha-glucosidase inhibitor, in type 2 diabetic patients on diet alone: results of a 24-week double-blind placebo-controlled study. *Diabetes Nutr Metab* 2002; **15:** 152–9.

Preparations
Proprietary Preparations (details are given in Part 3)

Austria: Diastabol; ***Cz.:*** Diastabol; ***Fr.:*** Diastabol; ***Ger.:*** Diastabol; ***Hung.:*** Diastabol; ***India:*** Diamig; Mignar†; ***Mex.:*** Diastabol; ***Neth.:*** Diastabol; ***Pol.:*** Diastabol; ***Port.:*** Diastabol; Limarcan; ***Spain:*** Diastabol; Plumarol; ***Swed.:*** Diastabol†; ***Switz.:*** Diastabol; ***USA:*** Glyset.

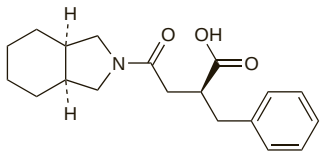
Mitiglinide *(rINN)*

Mitiglinida; Mitiglinidum. (–)-(2*S*,3a,7a-*cis*)-α-Benzylhexahydro-γ-oxo-2-isoindolinebutyric acid.

Митиглинид

$C_{19}H_{25}NO_3$ = 315.4.

CAS — 145375-43-5 (mitiglinide); 145525-41-3 (anhydrous mitiglinide calcium); 207844-01-7 (mitiglinide calcium dihydrate).



Profile
Mitiglinide is a meglitinide antidiabetic that is under investigation in the treatment of type 2 diabetes mellitus.

◊ References.

1. Yoshihara T, *et al.* Therapeutic efficacy of mitiglinide combined with once daily insulin glargine after switching from multiple daily insulin regimen of aspart insulin and glargine in patients with type 2 diabetes mellitus. *Endocr J* 2006; **53:** 67–72.

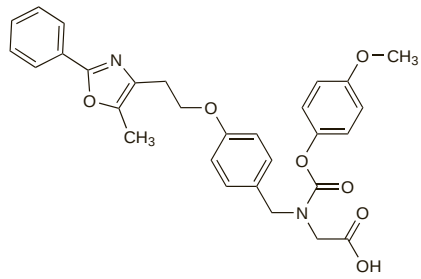
Muraglitazar *(USAN, rINN)*

BMS-298585; Muraglitazarum. {[(4-Methoxyphenoxy)carbonyl]{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}amino}acetic acid.

Мураглитазар

$C_{29}H_{28}N_2O_7$ = 516.5.

CAS — 331741-94-7.



Profile
Muraglitazar is a dual alfa/gamma peroxisome proliferator-activated receptor (PPAR) activator. It has been investigated in the treatment of type 2 diabetes mellitus.

Adverse effects. A review of data from 5 studies suggested that muraglitazar may be associated with an increased risk of adverse cardiovascular events and heart failure.[1]

1. Nissen SE, *et al.* Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005; **294:** 2581–6.

Nateglinide *(USAN, rINN)*

A-4166; AY-4166; DJN-608; Nateglinid; Nateglinida; Natéglinide; Nateglinidi; Nateglinidum; SDZ-DJN-608; Senaglinide; YM-026. (–)-*N*-[(*trans*-4-Isopropylcyclohexyl)carbonyl]-D-phenylalanine.

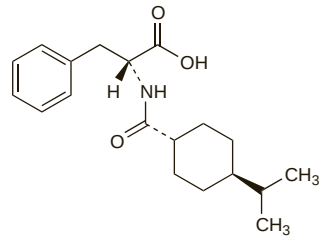
Нателинид

$C_{19}H_{27}NO_3$ = 317.4.

CAS — 105816-04-4.

ATC — A10BX03.

ATC Vet — QA10BX03.



Adverse Effects and Precautions
As for Repaglinide, p.457.

Overdosage. A blood-glucose concentration of 2.0 mmol/litre was measured 1 hour after ingestion of nateglinide 3.42 g in a 30-year-old woman.[1] She was able to walk unaided, but seemed drowsy. The hypoglycaemic effect of nateglinide lasted for 6 hours and was treated with intravenous glucose (total dose 100 g).

1. Nakayama S, *et al.* Hypoglycemia following a nateglinide overdose in a suicide attempt. *Diabetes Care* 2005; **28:** 227–8.

Renal impairment. A single-dose pharmacokinetic study[1] found that moderate to severe renal impairment (creatinine clearance 15 to 50 mL/minute per 1.73 m^2) and haemodialysis did not significantly affect the pharmacokinetics of nateglinide. However, the metabolite M1 has been found to accumulate in patients with renal impairment requiring haemodialysis after repeated doses of nateglinide, but it may be removed by haemodialysis.[2] M1 is a major metabolite that has modest hypoglycaemic activity compared with nateglinide. An analysis[3] of pooled study data found that efficacy and tolerability of nateglinide in elderly diabetic patients were not significantly affected by renal impairment (mean creatinine clearance 50.9 mL/minute per 1.73 m^2). Nevertheless, a 56-year-old diabetic woman whose renal failure was managed with haemodialysis experienced severe hypoglycaemia with nateglinide; the reaction was attributed to the accumulation of M1.[4] Licensed product information in the UK and USA suggest that no dosage adjustment is necessary in renal impairment, although UK information suggests that dose adjustment might be required in patients on haemodialysis.

1. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
2. Inoue T, *et al.* Pharmacokinetics of nateglinide and its metabolites in subjects with type 2 diabetes mellitus and renal failure. *Clin Nephrol* 2003; **60:** 90–5.
3. Del Prato S, *et al.* Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care* 2003; **26:** 2075–80.
4. Nagai T, *et al.* Hypoglycemia due to nateglinide administration in diabetic patient with chronic renal failure. *Diabetes Res Clin Pract* 2003; **59:** 191–4.

Interactions
As with other oral antidiabetics, the efficacy of nateglinide may be affected by drugs independently increasing or decreasing blood glucose concentrations (see Sulfonylureas, p.461).

◊ Reviews.

1. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. In a study[1] of healthy subjects, *rifampicin* reduced the plasma concentrations and half-life of nateglinide, probably by induction of its metabolism by the cytochrome P450 isoenzyme CYP2C9. The glucose-lowering effect of nateglinide was not affected, but there was a marked interindividual variation in the pharmacokinetic changes, and the authors suggested that some diabetic patients could be affected.

1. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of nateglinide in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 427–32.

Antifungals. In a study[1] of healthy subjects, *fluconazole* raised the plasma concentrations and prolonged the half-life of nateglinide, probably by inhibition of its metabolism by the cytochrome P450 isoenzyme CYP2C9. The glucose-lowering effect of nateglinide was not affected, but a low dose of nateglinide had been used and the authors suggested that in diabetic patients fluconazole may enhance and prolong the effects of nateglinide.

1. Niemi M, *et al.* Effect of fluconazole on the pharmacokinetics and pharmacodynamics of nateglinide. *Clin Pharmacol Ther* 2003; **74:** 25–31.

Lipid regulating drugs. A study[1] investigating the effects of the *gemfibrozil* and *itraconazole* combination on the pharmacokinetics of nateglinide showed only a limited interaction. Nateglinide plasma concentrations were raised moderately and the blood glucose response to nateglinide was not significantly changed. This is in contrast to the substantial interaction of gemfibrozil with repaglinide (p.458).

1. Niemi M, *et al.* Coadministration of gemfibrozil and itraconazole has only a minor effect on the pharmacokinetics of the CYP2C9 and CYP3A4 substrate nateglinide. *Br J Clin Pharmacol* 2005; **60:** 208–17.

Pharmacokinetics
Nateglinide is rapidly absorbed after oral doses, with peak plasma concentrations occurring within one hour and an absolute bioavailability of 73%. Nateglinide is 98% bound to plasma proteins. It is mainly metabolised by cytochrome P450 isoenzyme CYP2C9, and to a lesser extent by CYP3A4. Major metabolites include M1 which is less potent than nateglinide. The parent drug and metabolites are mainly excreted in the urine but about 10% is eliminated in the faeces. The elimination half-life is about 1.5 hours.

◊ References.

1. Choudhury S, *et al.* Single-dose pharmacokinetics of nateglinide in subjects with hepatic cirrhosis. *J Clin Pharmacol* 2000; **40:** 634–40.
2. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
3. McLeod JF. Clinical pharmacokinetics of nateglinide: a rapidly-absorbed, short-acting insulinotropic agent. *Clin Pharmacokinet* 2004; **43:** 97–120.

Uses and Administration
Nateglinide, like repaglinide (p.458), is a meglitinide antidiabetic used in the treatment of type 2 diabetes mellitus (p.431). It is given within the 30 minutes before meals in oral doses of 60 or 120 mg three times daily. This may be increased to 180 mg three times daily if necessary. Nateglinide is also given in similar doses with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by these drugs alone.

Although dose adjustment is not generally required in renal impairment, hypoglycaemia has been attributed to accumulation of the metabolite M1 (see above).

◊ References.

1. Dunn CJ, Faulds D. Nateglinide. *Drugs* 2000; **60:** 607–15.
2. Hanefeld M, *et al.* Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 2000; **23:** 202–7.
3. Horton ES, *et al.* Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 2000; **23:** 1660–5.

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.

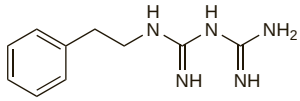
Multi-ingredient: ***Braz.:*** Starform; ***Venez.:*** Starform.

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†.

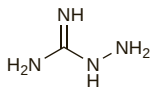
Multi-ingredient: ***Gr.:*** Daopar†; ***India:*** Chlorformin†; ***Ital.:*** Bi-Euglucon†; Bidiabe; Gliben F; Gliformin; Suguan†.

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.

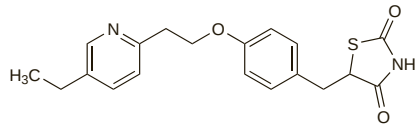
Pioglitazone Hydrochloride

(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)