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.

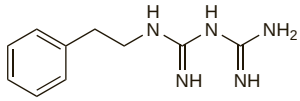
Multi-ingredient: ***Braz.:*** Starform; ***Venez.:*** Starform.

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†.

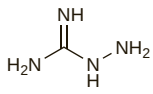
Multi-ingredient: ***Gr.:*** Daopar†; ***India:*** Chlorformin†; ***Ital.:*** Bi-Euglucon†; Bidiabe; Gliben F; Gliformin; Suguan†.

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.

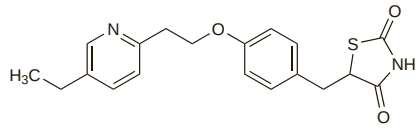
Pioglitazone Hydrochloride

(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)

Diabetic complications. It has been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications (p.433). Studies[1,2] in patients with type 2 diabetes mellitus have shown that pioglitazone may slow the progression of carotid intima-media thickness, an indicator for cardiovascular risk. A study[3] of secondary prevention found that, compared with placebo (in addition to usual medications for glucose control), pioglitazone reduced death from any cause, myocardial infarction, and stroke. There was also a reduced need to add insulin for glucose control. However, there was no significant difference between the groups when the end-point was broader and also included acute coronary syndrome, leg amputation, and coronary or leg revascularisation. Subgroup analysis[4] also found that pioglitazone reduced the risk of fatal and non-fatal myocardial infarction and acute coronary syndrome in patients with a history of myocardial infarction. A meta-analysis[5] that included the results of this study with cardiovascular outcome data from studies of glycaemic control found that pioglitazone significantly reduced the risk of death, myocardial infarction, and stroke in a diverse population of patients with type 2 diabetes. However, the risk of serious heart failure was increased (see also Effects on the Heart, p.459).

It is unclear whether other thiazolidinediones might have similar effects and whether patients at lower risk might benefit.[6] Rosiglitazone and pioglitazone are known to have different effects on lipids (above) and there is some evidence that rosiglitazone may have adverse cardiovascular effects (p.459).

1. Langenfeld MR, *et al.* Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. *Circulation* 2005; **111:** 2525–31.
2. Mazzone T, *et al.* Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; **296:** 2572–81.
3. Dormandy JA, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366:** 1279–89.
4. Erdmann E, *et al.* The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007; **49:** 1772–80.
5. Lincoff AM, *et al.* Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298:** 1180–8.
6. Rizza R, *et al.* Commentary on the results and clinical implications of the PROactive study. *Diabetes Care* 2005; **28:** 2965–7.

Hepatitis. A small proof-of-concept study has suggested that pioglitazone 45 mg daily with a hypocaloric diet for 6 months produces greater metabolic and histological improvement in patients with nonalcoholic steatohepatitis than diet alone.[1]

1. Belfort R, *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; **355:** 2297–2307.

Malignant neoplasms. For references to the experimental use of pioglitazone with rofecoxib and trofosfamide as anti-angiogenic therapy for malignant neoplasms see Trofosfamide, p.783.

Psoriasis. It has been suggested that by binding to peroxisome proliferator-activated receptor gamma, pioglitazone may have an anti-inflammatory effect in conditions such as chronic plaque psoriasis (p.1583) and psoriatic arthritis (see Spondyloarthropathies, p.13). In a small open-label study,[1] oral doses of 30 mg daily were reported to improve moderate chronic plaque psoriasis in 4 of 5 patients, with definite improvement seen 1 to 3 months after starting therapy. Treatment was stopped in 1 other patient because of fluid retention. In a double-blind study,[2] 70 patients with moderate to severe disease were treated for 10 weeks with daily doses of pioglitazone 15 mg, 30 mg, or placebo. Greater improvements were reported with pioglitazone than with placebo, and the dose of 30 mg appeared to be slightly more effective than 15 mg. There has also been a report[3] of improvements in tender and swollen joints in a small group of patients with psoriatic arthritis who were given a high dose of pioglitazone (30 mg twice daily) for 12 weeks. Fluid retention was also reported.

1. Robertshaw H, Friedmann PS. Pioglitazone: a promising therapy for psoriasis. *Br J Dermatol* 2005; **152:** 189–91.
2. Shafiq N, *et al.* Pilot trial: pioglitazone versus placebo in patients with plaque psoriasis (the P6). *Int J Dermatol* 2005; **44:** 328–33.
3. Bongartz T, *et al.* Treatment of active psoriatic arthritis with the PPARγ ligand pioglitazone: an open-label pilot study. *Rheumatology (Oxford)* 2005; **44:** 126–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Actos; Cereluc; Higlucem; Pioglit; Piotamax; ***Austral.:*** Actos; ***Austria:*** Actos; ***Belg.:*** Actos; ***Braz.:*** Actos; ***Canad.:*** Actos; ***Chile:*** Actos†; Diabestat†; Tiazac; ***Cz.:*** Actos; Glustin; ***Denm.:*** Actos; ***Fin.:*** Actos; ***Fr.:*** Actos; ***Ger.:*** Actos; ***Gr.:*** Actos; ***Hong Kong:*** Actos; ***India:*** Diaglit; G-Tase; Glita; Glizone; Opam; P-Glitz; Pepar; Piomed; Piosafe; Piozulin; ***Indon.:*** Actos; Deculin; ***Ital.:*** Actos; ***Jpn:*** Actos; ***Malaysia:*** Actos; ***Mex.:*** Zactos; ***Neth.:*** Actos; Glustin; ***Norw.:*** Actos; ***NZ:*** Actos; ***Philipp.:*** Actos; Prialta; Zypi; ***Port.:*** Actos; Glustin; ***Rus.:*** Actos (Актос); ***S.Afr.:*** Actos; ***Spain:*** Actos; ***Swed.:*** Actos; ***Switz.:*** Actos; ***Thai.:*** Actos; ***UK:*** Actos; ***USA:*** Actos; ***Venez.:*** Actos.

Multi-ingredient: ***Cz.:*** Competact; Glubrava; Tandemact; ***Fr.:*** Competact; Tandemact; ***India:*** Exermet P; P-Glitz M; Piomed M; Piosafe MF; ***Port.:*** Competact; Tandemact; ***UK:*** Competact; ***USA:*** Actoplus Met; Duetact.

Pramlintide *(BAN, USAN, rINN)*

AC-137; AC-0137 (pramlintide or pramlintide acetate); Pramlintida; Pramlintidum; Tripro-amylin.

Прамлинтид

$C_{171}H_{267}N_{51}O_{53}S_2$ = 3949.4.

CAS — 151126-32-8.

Pramlintide Acetate *(BANM, USAN, rINNM)*

AC-0137 (pramlintide or pramlintide acetate); Acetato de pramlintida; Pramlintide, Acétate de; Pramlintidi Acetas. 25-L-Proline-28-L-proline-29-L-prolineamylin (human) acetate hydrate.

Прамлинтида Ацетат

$C_{171}H_{267}N_{51}O_{53}S_2$, $xC_2H_4O_2$, yH_2O.

CAS — 196078-30-5.

Incompatibility. Pramlintide should not be mixed in the same syringe with insulin because of reported changes in the pharmacokinetic parameters of pramlintide.

Adverse Effects and Precautions

Pramlintide alone does not cause hypoglycaemia, but increases the risk associated with insulin use, particularly in type 1 diabetes mellitus; severe hypoglycaemia may occur within 3 hours of pramlintide injection. Blood-glucose concentrations must be closely monitored, both before and after meals, and the dose of insulin should be halved when pramlintide therapy is started (see Uses and Administration, below).

Other adverse effects of pramlintide include nausea, vomiting, anorexia, headache, reactions at the injection site, and hypersensitivity. Nausea commonly occurs at the beginning of therapy and decreases with time; incidence and severity are reduced if pramlintide is gradually titrated to the maintenance dose. Pramlintide is contra-indicated in patients with gastroparesis.

Interactions

Pramlintide has the potential to delay the absorption of oral medication; in cases where the rapid onset of action from an oral drug is critical, it should be given at least 1 hour before or 2 hours after pramlintide. Also, pramlintide may interfere with drugs given to alter gastrointestinal motility or absorption.

Pramlintide increases the risk of insulin-induced hypoglycaemia (see Adverse Effects and Precautions, above).

Pharmacokinetics

The bioavailability of pramlintide is about 30 to 40% from a subcutaneous injection. It is metabolised by the kidneys and has a half-life of about 48 minutes in healthy subjects.

Uses and Administration

Pramlintide is a synthetic analogue of amylin, a pancreatic peptide hormone thought to play a role in the regulation of glucose homoeostasis. It differs from amylin by replacement with proline at positions 25 (alanine), 28 (serine), and 29 (serine). Pramlintide slows the rate of gastric emptying, prevents the postprandial rise in glucagon concentrations, and reduces appetite. It is used in the management of diabetes mellitus (p.431) that is not adequately controlled by mealtime insulin therapy. Pramlintide is given as the acetate, but doses are expressed in terms of the base.

In patients with type 1 diabetes mellitus, an initial dose of pramlintide 15 micrograms is given subcutaneously immediately before major meals. The dose of any rapid-acting or short-acting insulins given before meals should be halved. The pramlintide dose may be increased in increments of 15 micrograms to a maintenance dose of 30 or 60 micrograms when no clinically significant nausea has occurred for at least 3 days. Once the maintenance dose of pramlintide has been achieved, the dose of insulin should be further adjusted for optimum glycaemic control.

In patients with type 2 diabetes mellitus who are using insulin, the initial dose of pramlintide is 60 micrograms, subcutaneously, immediately before major meals. The dose may be increased to 120 micrograms when no nausea has occurred for 3 to 7 days. The dose of insulin therapy should be adjusted as described for patients with type 1 diabetes mellitus (above).

◊ References.

1. Thompson RG, *et al.* Pramlintide, a synthetic analog of human amylin, improves the metabolic profile of patients with type 2 diabetes using insulin. *Diabetes Care* 1998; **21:** 987–93.
2. Whitehouse F, *et al.* A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care* 2002; **25:** 724–30.
3. Ratner RE, *et al.* Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther* 2002; **4:** 51–61.
4. Hollander PA, *et al.* Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2003; **26:** 784–90.
5. Kleppinger EL, Vivian EM. Pramlintide for the treatment of diabetes mellitus. *Ann Pharmacother* 2003; **37:** 1082–9.
6. Kruger DF, Gloster MA. Pramlintide for the treatment of insulin-requiring diabetes mellitus: rationale and review of clinical data. *Drugs* 2004; **64:** 1419–32.
7. Ratner RE, *et al.* Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004; **21:** 1204–12.
8. Ryan GJ, *et al.* Pramlintide in the treatment of type 1 and type 2 diabetes mellitus. *Clin Ther* 2005; **27:** 1500–12.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Symlin.

Repaglinide *(BAN, USAN, rINN)*

AG-EE-6232W; AG-EE-623-ZW; Repaglinid; Repaglinida; Repaglinidas; Répaglinide; Repaglinidi; Repaglinidum. (+)-2-Ethoxy-α-{[(*S*)-α-isobutyl-*o*-piperidinobenzyl]carbamoyl}-*p*-toluic acid; (*S*)-2-Ethoxy-4-{[1-(*o*-piperidinophenyl)-3-methylbutyl]carbamoylmethyl}benzoic acid.

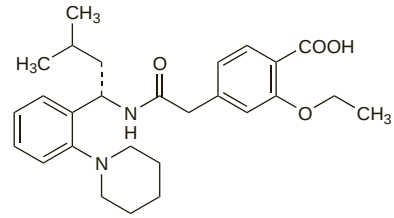
Репаглинид

$C_{27}H_{36}N_2O_4$ = 452.6.

CAS — 135062-02-1.

ATC — A10BX02.

ATC Vet — QA10BX02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Repaglinide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

USP 31 (Repaglinide). A white to off-white solid. Soluble in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

Repaglinide may cause gastrointestinal adverse effects including abdominal pain, diarrhoea, constipation, nausea, and vomiting. Hypoglycaemia (usually mild), back and joint pain, hypersensitivity reactions including pruritus, rashes and urticaria, and elevated liver enzyme values may occur. There have been rare cases of transient visual disturbances attributed to changes in blood glucose concentrations associated with starting repaglinide treatment. There have also been rare reports of myocardial infarction in patients who were treated with repaglinide and isophane insulin; the combination is not recommended.

Precautions are similar to those which apply with the shorter-acting sulfonylurea hypoglycaemics (p.461). Repaglinide should be given with caution to patients with hepatic impairment (consideration should be given to extending the interval between doses), and possibly avoided in severe impairment.

Effects on the liver. Hepatotoxic reactions have been reported for repaglinide[1,2] including cholestatic hepatitis and jaundice with pruritus.

1. Nan DN, *et al.* Acute hepatotoxicity caused by repaglinide. *Ann Intern Med* 2004; **141:** 823.
2. López-García F, *et al.* Cholestatic hepatitis associated with repaglinide. *Diabetes Care* 2005; **28:** 752–3.

Fasting. For mention that nateglinide or repaglinide can probably be used with low risk of hypoglycaemia in fasting Muslim patients during Ramadan see under Precautions of Insulin, p.448.

Hypoglycaemia. Mild hypoglycaemia has been reported in patients receiving repaglinide,[1] although in a study comparing flexible repaglinide dosing with fixed glibenclamide dosing, all hypoglycaemic events recorded were in the glibenclamide group.[2] Other studies have found rates of hypoglycaemia in patients receiving repaglinide to be less than, or similar to, sulfonylureas.[3] The risk of hypoglycaemia may be reduced as patients can omit a dose of repaglinide if a meal is missed.

1. Moses RG, *et al.* Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes Care* 2001; **24:** 11–15.