**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.

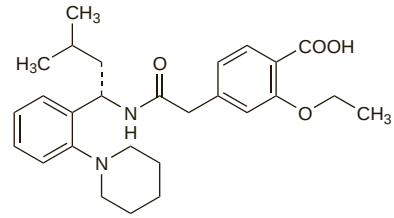
Репаглинид

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