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.

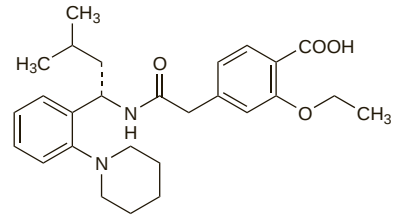
Репаглинид

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

2. Damsbo P, *et al.* A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care* 1999; **22:** 789–94.
3. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; **61:** 1625–60.

Pregnancy. Insulin is generally preferred to oral antidiabetics in the treatment of diabetes mellitus during pregnancy. Repaglinide has been used in 3 women during the first 6 to 7 weeks of gestation;[1,2] treatment was then changed to insulin for the rest of the pregnancy. Their babies were delivered at term, with adequate weight for birth age and no congenital malformations.

1. Napoli A, *et al.* Use of repaglinide during the first weeks of pregnancy in two type 2 diabetic women. *Diabetes Care* 2006; **29:** 2326–7.
2. Mollar-Puchades MA, *et al.* Use of repaglinide on a pregnant woman during embryogenesis. *Diabetes Obes Metab* 2007; **9:** 146–7.

Interactions

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

Drugs that affect the cytochrome P450 isoenzymes CYP2C8 and CYP3A4 may alter the metabolism of repaglinide. Use of repaglinide with the CYP2C8 inhibitor gemfibrozil has resulted in marked reduction in repaglinide clearance, and severe hypoglycaemia; UK licensed product information contra-indicates concomitant use.

◊ References.
1. Hatorp V, Thomsen MS. Drug interaction studies with repaglinide: repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. *J Clin Pharmacol* 2000; **40:** 184–92.
2. Hatorp V, *et al.* Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. *J Clin Pharmacol* 2003; **43:** 649–60.
3. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. A study[1] in healthy subjects found that the plasma concentration of a single dose of repaglinide was reduced, and its half-life shortened, when it was given 12.5 hours after the last dose of a 5-day course of *rifampicin*. This effect was attributed to the induction of the cytochrome P450 isoenzyme CYP3A4 by rifampicin. In another study[2] repaglinide was given either with the last dose of a 7-day course of rifampicin or 24 hours later, and the effects on repaglinide were found to be greater on day 8 than day 7. The authors suggested that rifampicin acted as both an inducer and an inhibitor of CYP3A4 and possibly CYP2C8, and that after rifampicin was stopped its inductive effect lasted longer, thereby having a greater effect 24 hours later.

A study[3] in healthy subjects reported that *clarithromycin* can increase the plasma concentrations and prolong the elimination half-life of repaglinide, probably by inhibition of CYP3A4. *Telithromycin*, another inhibitor of CYP3A4, also increased plasma concentrations of repaglinide in a study of healthy subjects, although the elimination half-life of repaglinide was not significantly affected.[4] *Trimethoprim*[5] can have a similar effect by the inhibition of CYP2C8.

For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving repaglinide, see p.281.

1. Niemi M, *et al.* Rifampin decreases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2000; **68:** 495–500.
2. Bidstrup TB, *et al.* Rifampicin seems to act as both an inducer and an inhibitor of the metabolism of repaglinide. *Eur J Clin Pharmacol* 2004; **60:** 109–14.
3. Niemi M, *et al.* The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2001; **70:** 58–65.
4. Kajosaari LI, *et al.* Telithromycin, but not montelukast, increases the plasma concentrations and effects of the cytochrome P450 3A4 and 2C8 substrate repaglinide. *Clin Pharmacol Ther* 2006; **79:** 231–42.
5. Niemi M, *et al.* The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. *Br J Clin Pharmacol* 2004; **57:** 441–7.

Ciclosporin. Ciclosporin markedly increased plasma concentrations of repaglinide in healthy subjects;[1] there is a possibly increased risk of hypoglycaemia if these 2 drugs are taken together.

1. Kajosaari LI, *et al.* Cyclosporine markedly raises the plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2005; **78:** 388–99.

Grapefruit juice. Grapefruit juice increased the bioavailability of repaglinide in a study of healthy subjects.[1] The half-life of repaglinide was not affected, suggesting that grapefruit juice inhibited its presystemic metabolism by the cytochrome P450 isoenzyme CYP3A4 in the gut wall. Blood-glucose concentrations were not affected.

1. Bidstrup TB, *et al.* The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. *Br J Clin Pharmacol* 2006; **61:** 49–57.

Lipid regulating drugs. A study[1] in healthy subjects found that *gemfibrozil* significantly increased the plasma concentrations of repaglinide and enhanced and prolonged its glucose-lowering effect. Use of this combination should be avoided. Another study[2] in healthy subjects found, however, that repaglinide was not affected by *bezafibrate* or *fenofibrate*.

1. Niemi M, *et al.* Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia* 2003; **46:** 347–51.
2. Kajosaari LI, *et al.* Lack of effect of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide. *Br J Clin Pharmacol* 2004; **58:** 390–6.

Pharmacokinetics

Repaglinide is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 hour. The mean bioavailability is about 60%. Repaglinide is highly bound to plasma proteins, and has a plasma elimination half-life of about 1 hour. It undergoes almost complete hepatic metabolism involving the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. The metabolites, which are inactive, are excreted in the bile. Higher plasma concentrations and prolonged half-life of repaglinide may occur in patients with renal impairment (creatinine clearance less than 40 mL/minute) or chronic liver disease.

◊ References.
1. Hatorp V, *et al.* Single-dose pharmacokinetics of repaglinide in subjects with chronic liver disease. *J Clin Pharmacol* 2000; **40:** 142–52.
2. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. *Clin Pharmacokinet* 2002; **41:** 471–83.
3. Bidstrup TB, *et al.* CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. *Br J Clin Pharmacol* 2003; **56:** 305–14.

Uses and Administration

Repaglinide is a meglitinide antidiabetic used for the treatment of type 2 diabetes mellitus (p.431). It has a chemical structure different from that of the sulfonylureas, but appears to have a similar mode of action.

Repaglinide is given up to 30 minutes before meals, in usual initial oral doses of 0.5 mg; initial doses of 1 or 2 mg are usually given to patients who have had previous hypoglycaemic treatment. The dose may be adjusted, at intervals of 1 to 2 weeks, up to a maximum of 4 mg before meals; a total of 16 mg daily should not be exceeded. Repaglinide is also given with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by monotherapy.

◊ References.
1. Anonymous. Repaglinide for type 2 diabetes mellitus. *Med Lett Drugs Ther* 1998; **40:** 55–6.
2. Moses R, *et al.* Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 1999; **22:** 119–24.
3. Wolffenbuttel BH, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care* 1999; **22:** 463–7.
4. 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.
5. Dornhorst A. Insulinotropic meglitinide analogues. *Lancet* 2001; **358:** 1709–16.
6. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; **61:** 1625–60.
7. Moses R. Repaglinide in combination therapy. *Diabetes Nutr Metab* 2002; **15** (suppl): 33–8.
8. Derosa G, *et al.* Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. *Clin Ther* 2003; **25:** 472–84.
9. Raskin P, *et al.* Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. *Diabet Med* 2004; **21:** 329–35.

Administration in renal impairment. Although repaglinide is cleared mainly by hepatic metabolism, small pharmacokinetic studies have reported that exposure to repaglinide may be increased in patients with renal impairment.[1,2] A larger open-label study[3] that included 151 patients with normal renal function and 130 patients with varying degrees of renal impairment found that the incidence of adverse effects was not influenced by renal function. However, at the end of the 3-month maintenance treatment period, there was a trend towards lower effective doses of repaglinide with increasing degree of renal impairment.

1. Marbury TC, *et al.* Pharmacokinetics of repaglinide in subjects with renal impairment. *Clin Pharmacol Ther* 2000; **67:** 7–15.
2. Schumacher S, *et al.* Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. *Eur J Clin Pharmacol* 2001; **57:** 147–52.
3. Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function. *Diabetes Care* 2003; **26:** 886–91.

Preparations

USP 31: Repaglinide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Glukenil; NovoNorm; Sestrine; ***Austral.:*** NovoNorm; ***Austria:*** NovoNorm; ***Belg.:*** NovoNorm; ***Braz.:*** Gluconorm; NovoNorm; Prandin; ***Canad.:*** Gluconorm; ***Chile:*** Hipover; NovoNorm; ***Cz.:*** NovoNorm; Prandin; ***Denm.:*** NovoNorm; ***Fin.:*** NovoNorm; ***Fr.:*** NovoNorm; ***Ger.:*** NovoNorm; ***Gr.:*** NovoNorm; ***Hong Kong:*** NovoNorm; ***Hung.:*** NovoNorm; ***India:*** Rapilin; ***Irl.:*** NovoNorm; ***Israel:*** NovoNorm; ***Ital.:*** NovoNorm; ***Malaysia:*** NovoNorm; ***Mex.:*** NovoNorm; ***Neth.:*** NovoNorm; Prandin; ***Norw.:*** NovoNorm; ***NZ:*** NovoNorm; ***Philipp.:*** NovoNorm; ***Pol.:*** NovoNorm; ***Port.:*** NovoNorm; Prandin; ***Rus.:*** NovoNorm (НовоНорм); ***S.Afr.:*** NovoNorm; ***Singapore:*** NovoNorm; ***Spain:*** NovoNorm; Prandin; ***Swed.:*** NovoNorm; ***Switz.:*** NovoNorm; ***Thai.:*** NovoNorm; ***Turk.:*** NovoNorm; ***UK:*** Prandin; ***USA:*** Prandin.

Rosiglitazone Maleate

(BANM, USAN, rINNM)

BRL-49653-C; Maleato de rosiglitazona; Rosiglitazone, Maléate de; Rosiglitazoni Maleas; Roziglitazon Maleat. (±)-5-{*p*-[2-(Methyl-2-pyridylamino)ethoxy]benzyl}-2,4-thiazolidinedione maleate (1:1).

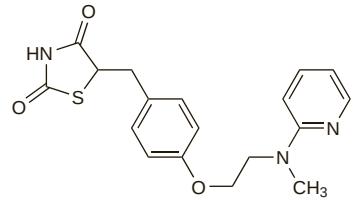
Розиглитазона Малеат

$C_{18}H_{19}N_3O_3S,C_4H_4O_4$ = 473.5.

CAS — 122320-73-4 (rosiglitazone); 155141-29-0 (rosiglitazone maleate); 316371-84-3 (rosiglitazone potassium).

ATC — A10BG02.

ATC Vet — QA10BG02.



(rosiglitazone)

Adverse Effects and Precautions

Rosiglitazone may cause hypoglycaemia, headache, weight gain, and anaemia. It may also cause dizziness, gastrointestinal disturbances, muscle cramps and myalgia, dyspnoea, paraesthesia, pruritus, and hypercholesterolaemia. Very rarely angioedema and urticaria have been reported. Rosiglitazone can also increase the risk of bone fracture in women.

Rosiglitazone can cause oedema, which may worsen or precipitate heart failure. It should therefore be used with caution in patients with oedema, and should not be used in those with a history of heart failure (see also below). Renal impairment may increase the risk of fluid retention and heart failure. There have been very rare reports of new onset and worsening diabetic macular oedema with decreased visual acuity (see Effects on the Eyes, below). There is some evidence to suggest that rosiglitazone might increase the risk of myocardial ischaemia; until further data become available, UK licensed product information advises that rosiglitazone is not recommended in patients with ischaemic heart disease or peripheral arterial disease (see also below). 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 Effects on the Liver, below).

In women who are anovulatory because of insulin resistance, rosiglitazone therapy may result in a resumption of ovulation.

Effects on the bones. Use of thiazolidinediones such as pioglitazone or rosiglitazone has been associated with decreases in bone mineral density and increased risk of fractures in female patients. Analysis of data from a comparative study[1] of glycaemic control with rosiglitazone, metformin, or glibenclamide involving 4360 randomised patients found that the risk of fracture in female patients in these 3 groups was 9.3%, 5.1%, and 3.5% respectively;[2] the risk in male patients was not significantly different in the 3 groups at around 3.4 to 3.95%. Analysis of data from another large ongoing study was also consistent with an in-