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).

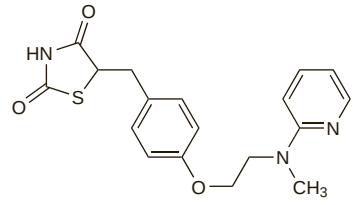
Розиглитазона Малеат

$C_{18}H_{19}N_3O_3S,C_4H_4O_4$ = 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-

creased fracture risk with rosiglitazone,[2] and data from the manufacturer of pioglitazone involving over 8100 treated patients also revealed an increased risk of fracture in women given the drug;[3] the excess risk was calculated to be 0.8 per 100 patient years of use. The pattern of fractures seems to differ from that associated with postmenopausal osteoporosis, being mainly in the upper arm, hand, or foot, rather than hip or spine, but an observational study has suggested that thiazolidinedione use is associated with ongoing loss of whole-body bone mineral density.[4]

1. Kahn SE, *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355:** 2427–43. Correction. *ibid.* 2007; **356:** 1387–8.
2. GSK, Canada. Increased incidence of fractures in female patients who received long-term treatment with Avandia (rosiglitazone maleate) tablets for type 2 diabetes mellitus (23rd February 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avandia_hpc-cps_3-eng.pdf (accessed 20/08/08)
3. Takeda, USA. Re observation of an increased incidence of fractures in female patients who received long-term treatment with Actos (pioglitazone HCl) tablets for type 2 diabetes mellitus (March 2007). Available at: http://www.fda.gov/medwatch/safety/2007/Actosmar0807.pdf (accessed 21/03/07)
4. Schwartz AV, *et al.* Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 2006; **91:** 3349–54.

Effects on the cardiovascular system. It has been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications, and there is some evidence that pioglitazone may improve some cardiovascular outcomes (see Diabetic Complications, p.457). However, a meta-analysis[1] of 42 studies found that, compared with either placebo or other antidiabetic drugs, rosiglitazone was associated with a significant increase in the risk of myocardial infarction, and an increase of borderline significance in death from cardiovascular causes. There were limitations to this analysis as the studies were not primarily intended to examine cardiovascular outcomes, and many were small and short-term. Another meta-analysis[2] that was restricted to 4 long-term studies (at least 12 months of treatment) that had specified an intention to evaluate cardiovascular adverse effects also found an increased risk of myocardial infarction with rosiglitazone use, without a significant increase in the risk of cardiovascular mortality.

Studies with no recorded cardiovascular events were excluded from the larger meta-analysis,[1] and this has been questioned. An alternative analysis[3] that incorporated these excluded studies, with appropriate analysis adjustment, found odds ratios for myocardial infarction and cardiovascular death that were not statistically significant, and concluded that neither increased nor decreased risk could be established.

In response to concerns raised by the initial meta-analysis, an unplanned interim analysis of an ongoing open-label study designed to assess cardiovascular outcomes has been published (rosiglitazone added to either metformin or a sulfonylurea compared with metformin plus a sulfonylurea).[4] The data, however, were insufficient to determine whether there was an increased risk of myocardial infarction, and the findings were inconclusive regarding any effect on overall risks of hospitalisation or death from cardiovascular causes.

For the risks of heart failure associated with thiazolidinediones, see Effects on the Heart, below.

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356:** 2457–71. Correction. *ibid.*; **357:** 100.
2. Singh S, *et al.* Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; **298:** 1189–95.
3. Diamond GA, *et al.* Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. *Ann Intern Med* 2007; **147:** 578–81.
4. Home PD, *et al.* RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 2007; **357:** 28–38.

Effects on the eyes. The manufacturers in the USA and Canada (*GSK*) have received postmarketing reports of the development or worsening of diabetic macular oedema in patients treated with rosiglitazone-containing products; in most cases the patients also reported peripheral oedema or fluid retention.[1,2] In some cases visual impairment improved or resolved after stopping the drug. Rosiglitazone should be used with caution in patients with pre-existing diabetic retinopathy or macular oedema, and should be stopped, and ophthalmological consultation sought, if visual impairment develops while using the drug.[2]

1. GSK, USA. Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin HCl): letter to healthcare professionals (issued December 2005). Available at: http://www.fda.gov/medwaTCH/safety/2006/Avandia_DHCPletter.pdf (accessed 03/05/06)
2. GSK, Canada. Association of Avandia and Avandamet with new onset and/or worsening of macular edema (issued 19th December, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avandia_avandamet_hpc-cps-eng.pdf (accessed 20/08/08)

Effects on the heart. Both pioglitazone and rosiglitazone can cause peripheral and pulmonary oedema, which can worsen or precipitate heart failure; a number of cases have been described.[1-6] A large retrospective cohort study[7] also found that the use of thiazolidinediones increased the risk of heart failure. The incidence of peripheral oedema with monotherapy has been reported[8] to range from 3 to 5%, and this increases slightly when a thiazolidinedione is used with another oral antidiabetic. The incidence is about 15% when a thiazolidinedione is used with insulin. The incidence of heart failure is generally lower, but has been reported to be 2 to 3% when a thiazolidinedione is used with insulin; however, a large prospective study,[9] which was intended to examine the cardiovascular benefits of pioglitazone in preventing secondary macrovascular events in diabetic patients with pre-existing macrovascular disease, reported a 6% incidence of heart failure, compared with 4% in the placebo group. Mortality rates from heart failure did not differ between groups. These figures were confirmed on re-analysis.[10]

The American Heart Association and American Diabetes Association have recommended[8] that patients with risk factors for heart disease or a depressed ejection fraction but without symptoms, and patients with NYHA class I or II heart failure, should start with a low dose of a thiazolidinedione that is only increased gradually as necessary and with careful monitoring. Patients with more severe heart failure (class III and IV) should not receive these drugs. These recommendations are reflected in US licensed product information. UK licensed product information contraindicates the use of pioglitazone or rosiglitazone in patients with heart failure or any history of heart failure, even of class I or II.

For restrictions on combination therapy see Administration, below.

1. Page RL, *et al.* Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. *Pharmacotherapy* 2003; **23:** 945–54.
2. Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc* 2003; **78:** 1088–91.
3. Bell DSH. Unilateral edema due to a thiazolidinedione. *Diabetes Care* 2003; **26:** 2700.
4. Shah M, *et al.* Pioglitazone-induced heart failure despite normal left ventricular function. *Am J Med* 2004; **117:** 973–4.
5. CSM/MHRA. Reminder: thiazolidinediones (glitazones) contraindications. *Current Problems* 2004; **30:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 02/06/06)
6. Cheng AYY, Fantus IG. Thiazolidinedione-induced congestive heart failure. *Ann Pharmacother* 2004; **38:** 817–20.
7. Delea TE, *et al.* Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2003; **26:** 2983–9.
8. Nesto RW, *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003; **108:** 2941–8. Also available at: http://circ.ahajournals.org/cgi/reprint/108/23/2941.pdf (accessed 26/03/07) Also published in *Diabetes Care* 2004; **27:** 256–63. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/1/256 (accessed 26/03/07)
9. 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.
10. Rydén L, *et al.* Adjudication of serious heart failure in patients from PROactive. *Lancet* 2007; **369:** 189–90.

Effects on lipids. Rosiglitazone and pioglitazone have different effects on serum lipids—see p.456.

Effects on the liver. Several cases of hepatotoxicity have been described[1-5] in patients receiving rosiglitazone. Most of these occurred within a few weeks or months of starting rosiglitazone therapy. However, the causality of some of these cases has been debated[6,7] because of coexisting disease and concomitant medication.

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

1. Forman LM, *et al.* Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med* 2000; **132:** 118–21.
2. Al-Salman J, *et al.* Hepatocellular injury in a patient receiving rosiglitazone: a case report. *Ann Intern Med* 2000; **132:** 121–4.
3. Ravinuthala RS, Nori U. Rosiglitazone toxicity. *Ann Intern Med* 2000; **133:** 658.
4. Hachey DM, *et al.* Isolated elevation of alkaline phosphatase level associated with rosiglitazone. *Ann Intern Med* 2000; **133:** 752.
5. Gouda HE, *et al.* Liver failure in a patient treated with long-term rosiglitazone therapy. *Am J Med* 2001; **111:** 584–5.
6. Freid J, *et al.* Rosiglitazone and hepatic failure. *Ann Intern Med* 2000; **132:** 164.
7. Isley WL, Oki JC. Rosiglitazone and liver failure. *Ann Intern Med* 2000; **133:** 393.

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

Interactions

Gemfibrozil, ketoconazole, and trimethoprim, can increase plasma concentrations of rosiglitazone. Conversely, rifampicin can reduce rosiglitazone concentrations. These drugs should be given with caution to patients taking rosiglitazone, and glycaemic control should be monitored.

Use of NSAIDs or insulin with rosiglitazone may increase the risk of oedema and heart failure (see also Effects on the Heart, above, and Administration, below).

Antibacterials. *Rifampicin* significantly reduced the plasma concentration and elimination half-life of rosiglitazone in studies[1,2] of healthy subjects, probably by induction of the cytochrome P450 isoenzyme CYP2C8. Conversely, *trimethoprim* can inhibit CYP2C8, and was found to increase the concentration and half-life of rosiglitazone modestly.[2,3]

1. Park J-Y, *et al.* Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004; **75:** 157–62.
2. Niemi M, *et al.* Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. *Clin Pharmacol Ther* 2004; **76:** 239–49.
3. Hruska MW, *et al.* The effect of trimethoprim on CYP2C8 mediated rosiglitazone metabolism in human liver microsomes and healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 70–9.

Antifungals. In a study[1] of healthy subjects, *ketoconazole* increased the plasma concentration and elimination half-life of rosiglitazone, probably by inhibition of the cytochrome P450 isoenzyme CYP2C8 and to a lesser extent CYP2C9.

1. Park J-Y, *et al.* Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 397–402.

Lipid regulating drugs. *Gemfibrozil* increased the plasma concentration and about doubled the half-life of rosiglitazone in a study[1] of healthy subjects, probably by inhibiting its metabolism. The authors suggested that these drugs should not be used together, or that the dose of rosiglitazone should be at least halved if gemfibrozil treatment is started.

1. Niemi M, *et al.* Gemfibrozil considerably increases the plasma concentrations of rosiglitazone. *Diabetologia* 2003; **46:** 1319–23.

Pharmacokinetics

Rosiglitazone is well absorbed from the gastrointestinal tract after oral dosing. Peak plasma concentrations occur within 1 hour and the bioavailability is 99%. It is 99.8% bound to plasma proteins. Rosiglitazone is extensively metabolised, almost exclusively by the cytochrome P450 isoenzyme CYP2C8. It is excreted in the urine and faeces, and has a half-life of 3 to 4 hours.

◊ References.

1. Baldwin SJ, *et al.* Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. *Br J Clin Pharmacol* 1999; **48:** 424–32.
2. Chapelsky MC, *et al.* Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. *J Clin Pharmacol* 2003; **43:** 252–9.

Uses and Administration

Rosiglitazone is a thiazolidinedione oral antidiabetic that improves insulin sensitivity and is used for the treatment of type 2 diabetes mellitus (p.431). It is usually given as rosiglitazone maleate but doses are expressed in terms of the base; rosiglitazone maleate 1.32 mg is equivalent to about 1 mg of rosiglitazone. The potassium salt is used in some countries. Rosiglitazone is given orally as monotherapy, particularly in patients who are overweight and for whom metformin is contra-indicated or not tolerated. It may also be added to metformin, a sulfonylurea (or a combination of the two), or to insulin, when such therapy is inadequate (but see Administration, below). The usual initial dose is 4 mg daily, given in a single dose or two divided doses. The dose may be increased to a maximum of 8 mg daily if necessary after 8 to 12 weeks in patients receiving monotherapy or combination oral therapy. Rosiglitazone may be taken with or without food.

◊ References.

1. Nolan JJ, *et al.* Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. *Diabet Med* 2000; **17:** 287–94.
2. Fonseca V, *et al.* Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000; **283:** 1695–1702. Correction. *ibid.*; **284:** 1384.
3. Lebovitz HE, *et al.* Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2001; **86:** 280–8.
4. Anonymous. Pioglitazone and rosiglitazone for diabetes. *Drug Ther Bull* 2001; **39:** 65–8.
5. Parulkar AA, *et al.* Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001; **134:** 61–71.
6. Raskin P, *et al.* A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care* 2001; **24:** 1226–32.
7. 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.

8. Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2002; **62:** 1805–37.
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10. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351:** 1106–18.
11. Dailey GE, *et al.* Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. *Am J Med* 2004; **116:** 223–9.
12. Czoski-Murray C, *et al.* Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation. *Health Technol Assess* 2004; **8:** 1–91.
13. Wellington K. Rosiglitazone/metformin. *Drugs* 2005; **65:** 1581–92.
14. Deeks ED, Keam SJ. Rosiglitazone : a review of its use in type 2 diabetes mellitus. *Drugs* 2007; **67:** 2747–79.

Administration. Although rosiglitazone is licensed for use with other antidiabetic drugs the specifics of licensing and use may vary from country to country. In both the UK and USA, rosiglitazone (*Avandia; GSK*) is licensed for use with metformin or a sulfonylurea, or both if necessary, in patients in whom single or dual agent therapy is inadequate. In the UK, however, NICE recommends dual therapy only in patients who cannot be given combination therapy with metformin plus a sulfonylurea.[1]

The combination of rosiglitazone with insulin is now generally avoided because of an increased risk of heart failure and other cardiac adverse events (see also Effects on the Heart, above), although licensed product information may not necessarily contraindicate the combination. In the UK, licensed product information for rosiglitazone warns that insulin should only be added to established rosiglitazone therapy in exceptional cases and under close supervision. In the USA, the combination of rosiglitazone and insulin is not recommended.

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/pdf/TA63_Glitazones_Review_Guidance.pdf (accessed 17/03/05)

Inflammatory bowel disease. There is some evidence[1] to suggest that drugs such as rosiglitazone that act as ligands to peroxisome proliferator-activated receptor γ (PPARγ) may offer a novel therapeutic approach to management of inflammatory bowel disease (p.1697).

1. Lewis JD, *et al.* Rosiglitazone for Ulcerative Colitis Study Group. Rosiglitazone for active ulcerative colitis: a randomized placebo-controlled trial. *Gastroenterology* 2008; **134:** 688–95.

Polycystic ovary syndrome. Insulin resistance is a feature of polycystic ovary syndrome (p.2080) and the use of rosiglitazone is under investigation.[1-3]

1. Baillargeon J-P, *et al.* Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. *Fertil Steril* 2004; **82:** 893–902.
2. Dereli D, *et al.* Endocrine and metabolic effects of rosiglitazone in non-obese women with polycystic ovary disease. *Endocr J* 2005; **52:** 299–308.
3. Yilmaz M, *et al.* The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. *Gynecol Endocrinol* 2005; **21:** 154–60.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Avandia; Diaben; Gaudil; Glimide; Gliximina; Gludex; Rosiglit; ***Austral.:*** Avandia; ***Belg.:*** Avandia; ***Braz.:*** Avandia; ***Canad.:*** Avandia; ***Chile:*** Avandia; ***Cz.:*** Avandia; ***Denm.:*** Avandia; ***Fin.:*** Avandia; ***Fr.:*** Avandia; ***Ger.:*** Avandia; ***Gr.:*** Avandia; ***Hong Kong:*** Avandia; ***Hung.:*** Avandia; ***India:*** Rezult†; Roglin; Rosicon; ***Indon.:*** Avandia; ***Irl.:*** Avandia; ***Israel:*** Avandia; ***Ital.:*** Avandia; ***Malaysia:*** Avandia; ***Mex.:*** Avandia; ***Neth.:*** Avandia; ***Norw.:*** Avandia; ***NZ:*** Avandia; ***Philipp.:*** Avandia; ***Pol.:*** Avandia; ***Port.:*** Avandia; ***Rus.:*** Avandia (Авандия); Roglit (Роглит); ***S.Afr.:*** Avandia; ***Singapore:*** Avandia; ***Spain:*** Avandia; ***Swed.:*** Avandia; ***Switz.:*** Avandia; ***Thai.:*** Avandia; ***Turk.:*** Avandia; ***UK:*** Avandia; ***USA:*** Avandia; ***Venez.:*** Avandia.

Multi-ingredient: ***Arg.:*** Avandamet; Gludex Plus; Rosiglit-Met; ***Austral.:*** Avandamet; ***Belg.:*** Avandamet; ***Canad.:*** Avandamet; ***Chile:*** Avandamet; ***Cz.:*** Avaglim; Avandamet; ***Denm.:*** Avandamet; ***Fin.:*** Avandamet; ***Fr.:*** Avaglim; Avandamet; ***Ger.:*** Avandamet; ***Gr.:*** Avaglim; Avandamet; ***Hong Kong:*** Avandamet; ***Hung.:*** Avaglim; Avandamet; ***India:*** Glyroz; Roglin-M; Rosicon MF; ***Indon.:*** Avandamet; Avandaryl; ***Irl.:*** Avandamet; ***Israel:*** Avandamet; ***Ital.:*** Avandamet; ***Malaysia:*** Avandamet; ***Mex.:*** Avandamet; ***Neth.:*** Avandamet; ***Norw.:*** Avandamet; ***Philipp.:*** Avandamet; ***Pol.:*** Avandamet; ***Port.:*** Avaglim; Avandamet; ***Singapore:*** Avandamet; ***Spain:*** Avandamet; ***Swed.:*** Avandamet; ***Switz.:*** Avandamet; ***Thai.:*** Avandamet; ***UK:*** Avandamet; ***USA:*** Avandamet; Avandaryl; ***Venez.:*** Avandamet.

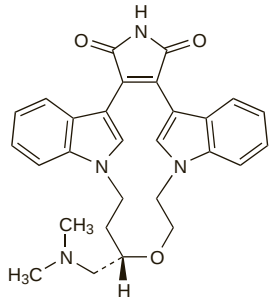
Ruboxistaurin *(rINN)*

LY-333531; LY-341684 (ruboxistaurin mesilate); Ruboxistaurina; Ruboxistaurine; Ruboxistaurinum. (9*S*)-9-[(Dimethylamino)methyl]-6,7,10,11-tetrahydro-9*H*,19*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-18,20-dione.

Рубоксистаурин

$C_{28}H_{28}N_4O_3$ = 468.5.

CAS — 169939-94-0 (ruboxistaurin); 169939-93-9 (ruboxistaurin hydrochloride); 202260-21-7 (ruboxistaurin mesilate).



Profile

Ruboxistaurin is an oral inhibitor of the β-isoform of the enzyme protein kinase C, which is thought to play a role in the development of diabetic microvascular complications (p.433). It is under investigation as an adjunct in the treatment of diabetic retinopathy.

◊ References.

1. Joy SV, *et al.* Ruboxistaurin, a protein kinase C β inhibitor, as an emerging treatment for diabetes microvascular complications. *Ann Pharmacother* 2005; **39:** 1693–9.
2. Vinik A. The protein kinase C-β inhibitor, ruboxistaurin, for the treatment of diabetic microvascular complications. *Expert Opin Invest Drugs* 2005; **14:** 1547–59.
3. The PKC-DRS Study Group. The effect of ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy: initial results of the Protein Kinase C β Inhibitor Diabetic Retinopathy Study (PKC-DRS) multicenter randomized clinical trial. *Diabetes* 2005; **54:** 2188–97.

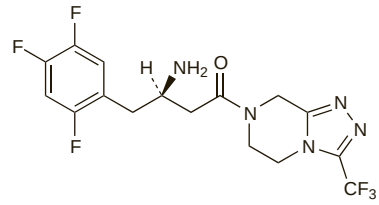
Sitagliptin Phosphate *(USAN, rINNM)*

Fosfato de sitagliptina; MK-431; MK-0431; Ono-5435; Sitagliptine, Phosphate de; Sitagliptini Phosphas. 7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazinemonophosphate monohydrate.

Ситаглиптина Фосфат

$C_{16}H_{15}F_6N_5O.H_3O_4P.H_2O$ = 523.3.

CAS — 486460-32-6 (sitagliptin); 654671-78-0 (sitagliptin phosphate); 654671-77-9 (sitagliptin phosphate monohydrate).



(sitagliptin)

Profile

Like vildagliptin (p.464), sitagliptin is an inhibitor of the enzyme dipeptidylpeptidase-4, an enzyme responsible, among other roles, for the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1; insulinotropin), which plays a role in regulating insulin secretion. It is used in the treatment of type 2 diabetes mellitus (p.431), as monotherapy or as dual therapy with metformin, a sulfonylurea, or a thiazolidinedione. Triple therapy using sitagliptin with metformin and a sulfonylurea may be given if dual therapy is inadequate. Sitagliptin is given as the phosphate, but doses are in terms of the base; 128.5 mg of sitagliptin phosphate is equivalent to about 100 mg of sitagliptin. The usual oral dose is the equivalent of 100 mg of sitagliptin once daily, as monotherapy or in combination. When given with metformin in a combination preparation, sitagliptin may be given in 2 divided doses. The dose of sulfonylurea may need to be lowered when used with sitagliptin. Sitagliptin may be taken with or without food. Dosage should be adjusted in patients with renal impairment (see below).

Adverse effects reported with sitagliptin include upper respiratory-tract infections, headache, and nasopharyngitis. Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, rash, and Stevens-Johnson syndrome have also been reported.

◊ References.

1. Herman GA,*et al.* Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. *Clin Pharmacol Ther* 2005; **78:** 675–88.
2. Bergman AJ, *et al.* Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. *Clin Ther* 2006; **28:** 55–72.
3. Aschner P, *et al.* Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006; **29:** 2632–7.
4. Charbonnel B, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006; **29:** 2638–43.
5. Rosenstock J, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 2006; **28:** 1556–68.
6. Brazg R, *et al.* Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabetes Obes Metab* 2007; **9:** 186–93.
7. Nauck MA, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2007; **9:** 194–205.
8. Scott R, *et al.* Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. *Int J Clin Pract* 2007; **61:** 171–80.
9. Deacon CF. Dipeptidyl peptidase 4 inhibition with sitagliptin: a new therapy for type 2 diabetes. *Expert Opin Invest Drugs* 2007; **16:** 533–545.
10. Lyseng-Williamson KA. Sitagliptin. *Drugs* 2007; **67:** 587–97.

Administration in renal impairment. US licensed product information suggests the following oral doses of sitagliptin in patients with renal impairment, based on creatinine clearance (CC):

- mild impairment (CC 50 mL/minute or more): no adjustment necessary, 100 mg daily
- moderate impairment (CC 30 to less than 50 mL/minute): 50 mg daily
- severe impairment (CC less than 30 mL/minute): 25 mg daily. It may be given without regard to the timing of haemodialysis

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Januvia; ***Braz.:*** Januvia; ***Cz.:*** Januvia; Tesavel; Xelevia; ***Fr.:*** Januvia; ***Gr.:*** Januvia; Xelevia; ***Malaysia:*** Januvia; ***Mex.:*** Januvia; ***Port.:*** Januvia; Tesavel; Xelevia; ***UK:*** Januvia; ***USA:*** Januvia.

Multi-ingredient: ***USA:*** Janumet.

Sulfonylurea Antidiabetics

Antidiabéticos sulfonilureas; Sulphonylurea Antidiabetics.

Adverse Effects

Gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, diarrhoea, and a metallic taste may occur with sulfonylureas and are usually mild and dose-dependent; increased appetite and weight gain may occur. Skin rashes and pruritus may occur and photosensitivity has been reported. Rashes are usually hypersensitivity reactions and may progress to more serious disorders (see below). Facial flushing may develop in patients receiving sulfonylureas, particularly chlorpropamide, when alcohol is consumed (see under Interactions, below).

Mild hypoglycaemia may occur; severe hypoglycaemia is usually an indication of overdosage and is relatively uncommon. Hypoglycaemia is more likely with long-acting sulfonylureas such as chlorpropamide and glibenclamide, which have been associated with severe, prolonged, and sometimes fatal hypoglycaemia.

Other severe effects may be manifestations of a hypersensitivity reaction. They include altered liver enzyme values, hepatitis and cholestatic jaundice, leucopenia, thrombocytopenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, erythema multiforme or the Stevens-Johnson syndrome, exfoliative dermatitis, and erythema nodosum.

The sulfonylureas, particularly chlorpropamide, occasionally induce a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) characterised by water retention, hyponatraemia, and CNS effects. However, some sulfonylureas, such as glibenclamide, glipizide, and tolazamide are also stated to have mild diuretic actions.