8. Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2002; **62:** 1805–37.
9. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. *Drugs* 2003; **63:** 1373–1405.
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.

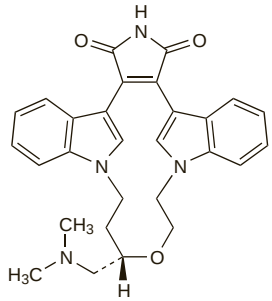
Ruboxistaurin *(rINN)*

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.

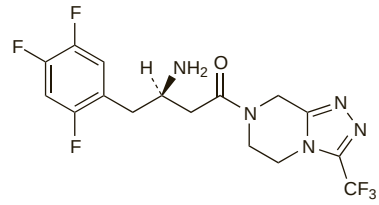
Sitagliptin Phosphate *(USAN, rINNM)*

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.