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.

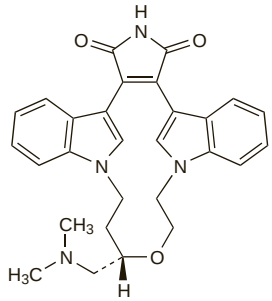
Ruboxistaurin *(rINN)*

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.

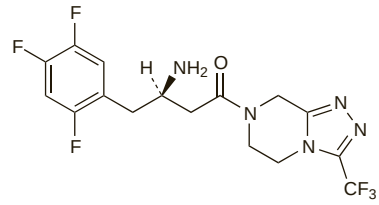
Sitagliptin Phosphate *(USAN, rINNM)*

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.

Work on tolbutamide has suggested that the sulfonylureas might be associated with an increase in cardiovascular mortality; this has been the subject of considerable debate (see Effects on the Cardiovascular System, below).

◊ Reviews.

1. Paice BJ, *et al*. Undesired effects of the sulphonylurea drugs. *Adverse Drug React Acute Poisoning Rev* 1985; **4:** 23–36.
2. Harrower ADB. Comparative tolerability of sulphonylureas in diabetes mellitus. *Drug Safety* 2000; **22:** 313–20.

Effects on the cardiovascular system. A multicentre study carried out under the University Group Diabetes Program (UGDP) reported an increased incidence in mortality from cardiovascular complications in diabetic patients given tolbutamide as compared with those treated with diet alone or insulin;[1] a similar increase was also noted in patients given phenformin.[2] The reports from the UGDP aroused prolonged controversy which was not entirely settled by detailed reassessment of relevant studies.[3] Eventually in 1984 the FDA made it a requirement that sulfonylurea oral antidiabetics be labelled with a specific warning about the possibility of increased cardiovascular mortality associated with the use of these drugs.[4] Subsequently the cardiovascular effects of the sulfonylureas were reviewed.[5] It has been hypothesised that the action of the sulfonylureas in preventing the opening of ATP-sensitive potassium channels in the myocardium may abolish adaptive changes (ischaemic preconditioning) that protect the heart against ischaemic insult.[6] A recent retrospective cohort study has also found that, among patients newly treated for type 2 diabetes, sulfonylurea monotherapy was associated with an increased mortality compared with metformin therapy.[7] However, results from the UK Prospective Diabetes Study did not demonstrate any adverse cardiovascular effects associated with sulfonylurea therapy.[8]

1. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes III: clinical implications of UGDP results. *JAMA* 1971; **218:** 1400–10.
2. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes IV: a preliminary report on phenformin results. *JAMA* 1971; **217:** 777–84.
3. Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. *JAMA* 1975; **231:** 583–600.
4. FDA. Class labeling for oral hypoglycemics. *FDA Drug Bull* 1984; **14:** 16–17.
5. Huupponen R. Adverse cardiovascular effects of sulphonylurea drugs: clinical significance. *Med Toxicol* 1987; **2:** 190–209.
6. Yellon DM, *et al*. Angina reassessed: pain or protector? *Lancet* 1996; **347:** 1159–62.
7. Simpson SH, *et al.* Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *Can Med Assoc J* 2006; **174:** 169–74.
8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid.* 1999; **354:** 602.

Effects on the eyes. When a diabetic patient who had experienced bilateral visual loss for several months and who had been taking chlorpropamide for one year stopped treatment, visual acuity improved and colour vision rapidly returned.[1] A 5-day challenge with chlorpropamide resulted in a mild decrease in acuity followed by return to baseline values when treatment was again stopped. Drug-induced optic neuropathy was considered to have occurred. There is also a report of a patient with type 2 diabetes mellitus who developed myopia two days after starting treatment with glibenclamide 10 mg daily.[2] Visual difficulties resolved a few days after stopping glibenclamide.

1. Wymore J, Carter JE. Chlorpropamide-induced optic neuropathy. *Arch Intern Med* 1982; **142:** 381.
2. Teller J, *et al.* Accommodation insufficiency induced by glybenclamide. *Ann Ophthalmol* 1989; **21:** 275–6.

Effects on the kidneys. The nephrotic syndrome has been reported in a patient treated with chlorpropamide.[1] Serological testing and renal biopsy showed that the glomerular lesions were of an immune-complex nature. Both the nephrotic syndrome and the glomerulonephritis resolved after treatment was stopped. The patient also developed a skin eruption, hepatitis, and eosinophilia.

1. Appel GB, *et al*. Nephrotic syndrome and immune complex glomerulonephritis associated with chlorpropamide therapy. *Am J Med* 1983; **74:** 337–42.

Effects on the liver. Chlorpropamide was implicated[1] in 8 of 53 cases of drug-induced acute liver disease admitted to a hospital in Jamaica over the years 1973 to 1988. Hepatocanalicular cholestasis occurred in 5 cases and diffuse necrosis in 3. One patient with massive hepatic necrosis died. Intrahepatic cholestasis,[2-4] an acute hepatitis-like syndrome,[5] and a combination of both[6] have been described in patients receiving glibenclamide.

1. Lee MG, *et al*. Drug-induced acute liver disease. *Postgrad Med J* 1989; **65:** 367–70.
2. Wongpaitoon V, *et al*. Intrahepatic cholestasis and cutaneous bullae associated with glibenclamide therapy. *Postgrad Med J* 1981; **57:** 244–6.
3. Krivoy N, *et al*. Fatal toxic intrahepatic cholestasis secondary to glibenclamide. *Diabetes Care* 1996; **19:** 385–6.
4. Tholakanahalli VN, *et al.* Glibenclamide-induced cholestasis. *West J Med* 1998; **168:** 274–7.
5. Goodman RC, *et al.* Glyburide-induced hepatitis. *Ann Intern Med* 1987; **106:** 837–9.
6. Petrogiannopoulos C, Zacharof A. Glibenclamide and liver disease. *Diabetes Care* 1997; **20:** 1215.

Effects on the thyroid. See under Precautions, below.

Hypoglycaemia. Severe hypoglycaemia may occur in any patient treated with any sulfonylurea; this potentially life-threatening complication requires prolonged and energetic treatment.[1] Sulfonylureas with a prolonged duration of action such as chlorpropamide and glibenclamide appear to cause severe hypoglycaemia more often than shorter-acting drugs such as tolbutamide. Experience with newer drugs is limited.

A review of 1418 cases of drug-induced hypoglycaemia reported since 1940 showed that sulfonylureas (especially chlorpropamide and glibenclamide), either alone or with a second antidiabetic or potentiating agent, accounted for 63% of all cases.[2] A study of sulfonylurea use in nearly 14,000 patients aged 65 years or older confirmed that chlorpropamide and glibenclamide were associated with hypoglycaemia. However, glipizide caused significantly fewer cases than glibenclamide.[3]

An analysis,[4] of 185 children reported to 10 regional poison centres in the USA after ingesting sulfonylureas found that hypoglycaemia developed only in 56. A lack of hypoglycaemia during the first 8 hours after ingestion was predictive of a benign outcome, and it was recommended that suspected cases be observed for 8 hours with frequent blood glucose monitoring. Children who developed signs of hypoglycaemia, or in whom blood glucose fell below 3.3 mmol/litre could be given intravenous glucose if necessary.

See also under Abuse, below.

1. Ferner RE, Neil HAW. Sulphonylureas and hypoglycaemia. *BMJ* 1988; **296:** 949–50.
2. Seltzer HS. Drug-induced hypoglycaemia. *Endocrinol Metab Clin North Am* 1989; **18:** 163–83.
3. Shorr RI, *et al.* Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 1996; **44:** 751–5.
4. Spiller HA, *et al.* Prospective multicenter study of sulfonylurea ingestion in children. *J Pediatr* 1997; **131:** 141–6.

Treatment of Adverse Effects

In acute poisoning with sulfonylureas, if the patient is conscious and presents within 1 hour of ingestion, the stomach should be emptied and/or activated charcoal given. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p.447). The patient should be observed over several days in case hypoglycaemia recurs. Octreotide has been used in the treatment of severe refractory cases of sulfonylurea-induced hypoglycaemia.

◊ References.

1. Spiller HA. Management of antidiabetic medication in overdose. *Drug Safety* 1998; **19:** 411–24.
2. McLaughlin SA, *et al.* Octreotide: an antidote for sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 2000; **36:** 133–8.
3. Carr R, Zed PJ. Octreotide for sulfonylurea-induced hypoglycemia following overdose. *Ann Pharmacother* 2002; **36:** 1727–32.

Precautions

Sulfonylureas should not be used in type 1 diabetes mellitus. Use in type 2 diabetes mellitus is contra-indicated in patients with ketoacidosis and in those with severe infection, trauma, or other severe conditions where the sulfonylurea is unlikely to control the hyperglycaemia; insulin should be used in such situations.

Insulin is also preferred for therapy during pregnancy.

Sulfonylureas with a long half-life such as chlorpropamide or glibenclamide are associated with an increased risk of hypoglycaemia. They should therefore be avoided in patients with impairment of renal or hepatic function, and a similar precaution would tend to apply in other groups with an increased susceptibility to this effect, such as the elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency. Irregular mealtimes, missed meals, changes in diet, or prolonged exercise may also provoke hypoglycaemia. Where a sulfonylurea needs to be used in patients at increased risk of hypoglycaemia, a short-acting drug such as tolbutamide or gliclazide may be preferred; these 2 sulfonylureas, being principally inactivated in the liver, are perhaps particularly suitable in renal impairment, although careful monitoring of blood-glucose concentration is essential.

Abuse. Severe hypoglycaemia, at first thought to be due to insulinoma but later found to be due to nesidioblastosis [proliferation of the islet cells], was reported in a woman covertly taking chlorpropamide.[1]

1. Rayman G, *et al*. Hyperinsulinaemic hypoglycaemia due to chlorpropamide-induced nesidioblastosis. *J Clin Pathol* 1984; **37:** 651–4.

Administration. It has been suggested that continuously high plasma concentrations of sulfonylureas may lead to the development of tolerance, and that therefore the maximum recommended doses should be reduced.[1]

1. Melander A, *et al.* Is there a concentration-effect relationship for sulphonylureas? *Clin Pharmacokinet* 1998; **34:** 181–8.

Breast feeding. Some sulfonylureas are distributed into breast milk and the class of drugs should be avoided during breast feeding.

Driving. In the UK, patients with diabetes mellitus treated with insulin or oral hypoglycaemics are required to notify their condition to the Driver and Vehicle Licensing Agency, who then assess their fitness to drive. Patients treated with oral hypoglycaemics are generally allowed to retain standard driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years. Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur. Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (field of vision of at least 120°) for a licence to be valid. Patients treated with diet or oral hypoglycaemics are normally allowed to hold vocational driving licences for heavy goods vehicles or passenger carrying vehicles; those treated with insulin may not drive such vehicles, and are restricted in driving some other vehicles such as small lorries and minibuses.

References.

1. British Diabetic Association (Diabetes UK). Information sheet: driving and diabetes: May 2008. Available at: http://www.diabetes.org.uk/Documents/catalogue/driving_and_diabetes-may_08.pdf (accessed 20/08/08)
2. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

Fasting. For the suggestion that sulfonylureas should be used with caution in fasting Muslim patients during Ramadan, and that chlorpropamide is contra-indicated in this group, see under Precautions of Insulin, p.448.

Porphyria. Sulfonylureas have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.

Thyroid disorders. There are conflicting reports concerning the effects of sulfonylureas on thyroid function, with some studies suggesting an increased incidence of thyroid dysfunction in patients treated with tolbutamide or chlorpropamide,[1] while other suggest no antithyroid action.[2,3] Some licensed product information consequently recommends that chlorpropamide should be avoided in patients with impaired thyroid function. Changes in thyroid function may conversely affect glycaemic control—for mention of the possible effects of thyroid hormones on antidiabetic drug requirements see under Interactions, below.

1. Hunton RB, *et al.* Hypothyroidism in diabetics treated with sulphonylurea. *Lancet* 1965; **ii:** 449–51.
2. Burke G, *et al.* Effect of long-term sulfonylurea therapy on thyroid function in man. *Metabolism* 1967; **16:** 651–7.
3. Feely J, *et al.* Antithyroid effect of chlorpropamide? *Hum Toxicol* 1983; **2:** 149–53.

Interactions

Many interactions have been reported with the sulfonylureas, largely representing either pharmacokinetic interactions (due to the displacement of the antidiabetic from plasma proteins or alteration in its metabolism or excretion) or pharmacological interactions with drugs having an independent effect on blood glucose. In the former class most reports concern older sulfonylureas such as chlorpropamide and tolbutamide, although the possibility of such reactions with newer drugs should be borne in mind.

A diminished hypoglycaemic effect, possibly requiring an increased dose of sulfonylurea, has been seen or might be expected on theoretical grounds with adrenaline, aminoglutethimide, chlorpromazine, corticosteroids, diazoxide, oral contraceptives, rifamycins, thiazide diuretics, and thyroid hormones.

An increased hypoglycaemic effect has occurred or might be expected with ACE inhibitors, alcohol, allopurinol, some analgesics (notably azapropazone, phenylbutazone, and the salicylates), azole antifungals (fluconazole, ketoconazole, and miconazole), chloramphenicol, cimetidine, clofibrate and related compounds, coumarin anticoagulants, fluoroquinolones, heparin, MAOIs, octreotide (although this may also produce hyperglycaemia), ranitidine, sulfinpyrazone, sulfonamides (including co-trimoxazole), tetracyclines, and tricyclic antidepressants.

Beta blockers have been reported both to increase hypoglycaemia and to mask the typical sympathetic warning signs. There are sporadic and conflicting reports of a possible interaction with calcium-channel blockers, but overall any effect seems to be of little clinical significance.

In addition to producing hypoglycaemia alcohol can interact with chlorpropamide to produce an unpleasant flushing reaction. Such an effect is rare with other sulfonylureas and alcohol.

◊ General references.

1. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part I). *Drugs* 1990; **40:** 6–18.
2. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part II). *Drugs* 1990; **40:** 203–19.
3. Girardin E, *et al.* Hypoglycémies induites par les sulfamides hypoglycémiants. *Ann Med Interne (Paris)* 1992; **143:** 11–17.

ACE inhibitors. There are sporadic reports of marked hypoglycaemia developing in patients taking a sulfonylurea who are given an ACE inhibitor (mainly *captopril* or *enalapril*),[1-3] and 2 case-control studies have indicated that the combination is associated with an increased risk of developing severe hypoglycaemia.[4,5] However, other studies have failed to find much evidence of a problem.[6-9]

1. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
2. Rett K, *et al.* Hypoglycemia in hypertensive diabetic patients treated with sulfonylureas, biguanides, and captopril. *N Engl J Med* 1988; **319:** 1609.
3. Arauz-Pacheco C, *et al.* Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. *Am J Med* 1990; **89:** 811–13.
4. Herings RMC, *et al.* Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345:** 1195–8.
5. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
6. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
7. Passa P, *et al.* Enalapril, captopril, and blood glucose. *Lancet* 1986; **i:** 1447.
8. Winocour P, *et al.* Captopril and blood glucose. *Lancet* 1986; **ii:** 461.
9. Shorr RI, *et al.* Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 1997; **278:** 40–3.

Alcohol. Sulfonylurea-induced alcohol intolerance is seen mainly but not exclusively with chlorpropamide; this is similar to the disulfiram-alcohol interaction, although it is not clear whether the mechanism is the same. Since the main symptom of the reaction (facial flushing) appears to occur more commonly in diabetic than non-diabetic subjects, it has been proposed that this symptom could be used as a diagnostic test for a certain subset of patients with type 2 diabetes mellitus.[1,2] However, some have not considered the test to be sufficiently specific[3-6] and despite a great deal having been published on the chlorpropamide-alcohol flushing test (CPAF), its value remains poorly defined. Alcohol, as well as provoking a flushing reaction with chlorpropamide, has been reported both to increase and to decrease the half-life of tolbutamide depending on whether the alcohol administration was acute or chronic.[7] Alcohol may also have a variable effect of its own on blood-glucose concentrations; there is a general tendency to increased hypoglycaemia when alcohol and sulfonylureas are taken concurrently.[6]

1. Leslie RDG, Pyke DA. Chlorpropamide-alcohol flushing: a dominantly inherited trait associated with diabetes. *BMJ* 1978; **2:** 1519–21.
2. Pyke DA, Leslie RDG. Chlorpropamide-alcohol flushing: a definition of its relation to non-insulin-dependent diabetes. *BMJ* 1978; **2:** 1521–2.
3. de Silva NE, *et al.* Low incidence of chlorpropamide-alcohol flushing in diet-treated, non-insulin-dependent diabetes. *Lancet* 1981; **i:** 128–31.
4. Fui SNT, *et al.* Epidemiological study of prevalence of chlorpropamide alcohol flushing in insulin dependent diabetes, non-insulin dependent diabetics, and non-diabetics. *BMJ* 1983; **287:** 1509–12.
5. Fui SNT, *et al.* Test for chlorpropamide-alcohol flush becomes positive after prolonged chlorpropamide treatment in insulin-dependent and non-insulin-dependent diabetics. *N Engl J Med* 1983; **309:** 93–6.
6. Lao B, *et al.* Alcohol tolerance in patients with non-insulin-dependent (type 2) diabetes treated with sulphonylurea derivatives. *Arzneimittelforschung* 1994; **44:** 727–34.
7. Sellers EM, Holloway MR. Drug kinetics and alcohol ingestion. *Clin Pharmacokinet* 1978; **3:** 440–52.

Analgesics. *Phenylbutazone*[1,2] and related drugs such as *azapropazone*[3] have been associated with acute hypoglycaemic episodes when given to patients receiving sulfonylureas (in most reports, tolbutamide). Other analgesics may enhance the hypoglycaemic effect of sulfonylureas, including *indobufen*,[4] *fenclofenac*,[5] and the *salicylates*.[6,7] Although a study in healthy subjects found no interaction,[7] there has been a report of hypoglycaemia with *ibuprofen* in a diabetic patient who had been stabilised on glibenclamide.[8]

1. Tannenbaum H, *et al.* Phenylbutazone-tolbutamide drug interaction. *N Engl J Med* 1974; **290:** 344.
2. Dent LA, Jue SG. Tolbutamide-phenylbutazone interaction. *Drug Intell Clin Pharm* 1976; **10:** 711.
3. Andreasen PB, *et al.* Hypoglycaemia induced by azapropazone-tolbutamide interaction. *Br J Clin Pharmacol* 1981; **12:** 581–3.
4. Elvander-Ståhl E, *et al.* Indobufen interacts with the sulphonylurea, glipizide, but not with the β-adrenergic receptor antagonists, propranolol and atenolol. *Br J Clin Pharmacol* 1984; **18:** 773–8.
5. Allen PA, Taylor RT. Fenclofenac and thyroid function tests. *BMJ* 1980; **281:** 1642.
6. Richardson T, *et al.* Enhancement by sodium salicylate of the blood glucose lowering effect of chlorpropamide—drug interaction or summation of similar effects? *Br J Clin Pharmacol* 1986; **22:** 43–8.
7. Kubacka RT, *et al.* Effects of aspirin and ibuprofen on the pharmacokinetics and pharmacodynamics of glyburide in healthy subjects. *Ann Pharmacother* 1996; **30:** 20–6.
8. Sone H, *et al.* Ibuprofen-related hypoglycemia in a patient receiving sulfonylurea. *Ann Intern Med* 2001; **134:** 344.

Antibacterials. *Chloramphenicol* markedly inhibits the metabolism of tolbutamide and increases its half-life,[1] which can result in hypoglycaemia. Sulfonamides,[2] including *co-trimoxazole*,[3-5] may also enhance the hypoglycaemic effects of the sulfonylureas. There have been rare reports of elevated glibenclamide concentrations and hypoglycaemia when *ciprofloxacin* was given to patients who were on stable glibenclamide therapy.[6] For reports of hypoglycaemia when *gatifloxacin* was given to patients already receiving a sulfonylurea (glimepiride in one case, and glibenclamide plus pioglitazone in another), see p.281. There have also been a few cases of severe hypoglycaemia when *clarithromycin* was added to glibenclamide or glipizide; renal impairment may have played a role in these cases.[7] *Rifampicin* (and probably other rifamycins) can enhance the metabolism and decrease the effect of tolbutamide, chlorpropamide,[8,9] and glibenclamide[10] and dosage of the hypoglycaemic drug may need to be increased. The effects on glipizide[10] and glimepiride[11] appear to be less pronounced.

1. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; **ii:** 1397–9.
2. Soeldner JS, Steinke J. Hypoglycemia in tolbutamide-treated diabetes: report of two cases with measurement of serum insulin. *JAMA* 1965; **193:** 148–9.
3. Wing LMH, Miners JO. Cotrimoxazole as an inhibitor of oxidative drug metabolism: effects of trimethoprim and sulphamethoxazole separately and combined on tolbutamide disposition. *Br J Clin Pharmacol* 1985; **20:** 482–5.
4. Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. *DICP Ann Pharmacother* 1990; **24:** 250–1.
5. Abad S, *et al.* Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; **52:** 456–7.
6. Roberge RJ, *et al.* Glyburide-ciprofloxacin interaction with resistant hypoglycemia. *Ann Emerg Med* 2000; **36:** 160–3.
7. Bussing R, Gende A. Severe hypoglycemia from clarithromycin-sulfonylurea drug interaction. *Diabetes Care* 2002; **25:** 1659–61.
8. Syvälahti EKG, *et al.* Rifampicin and drug metabolism. *Lancet* 1974; **ii:** 232–3.
9. Self TH, Morris T. Interaction of rifampin and chlorpropamide. *Chest* 1980; **77:** 800–1.
10. Niemi M, *et al.* Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. *Clin Pharmacol Ther* 2001; **69:** 400–406.
11. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride. *Br J Clin Pharmacol* 2000; **50:** 591–5.

Anticoagulants. *Dicoumarol* increases serum concentrations and therefore the hypoglycaemic effects of tolbutamide, and possibly chlorpropamide. In addition, sulfonylureas may affect anticoagulant function (p.1428).

Antiepileptics. For references to *phenytoin* toxicity when tolbutamide or tolazamide was given, see under Phenytoin p.498.

Antifungals. Increased plasma concentrations of tolbutamide have been reported when *fluconazole* was given,[1] but there was no evidence of hypoglycaemia, and no hypoglycaemic symptoms were seen in 29 women receiving gliclazide or glibenclamide who were given fluconazole or *clotrimazole* for vulvovaginitis.[2] A study in healthy subjects found that fluconazole increased plasma concentrations of glimepiride, but again there was no significant effect on glucose concentrations.[3] However, there are reports of hypoglycaemia in a patient who took fluconazole with glipizide,[4] and another who took fluconazole and co-trimoxazole with gliclazide.[5] Similar interactions have been reported for *ketoconazole* (with tolbutamide, in healthy subjects)[6] and *miconazole* (with tolbutamide, in a diabetic),[7] suggesting that such combinations should be regarded with caution.

1. Lazar JD, Wilner DK. Drug interactions with fluconazole. *Rev Infect Dis* 1990; **12** (suppl 3): S327–S333.
2. Rowe BR, *et al.* Safety of fluconazole in women taking oral hypoglycaemic agents. *Lancet* 1992; **339:** 255–6.
3. Niemi M, *et al.* Effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. *Clin Pharmacol Ther* 2001; **69:** 194–200.
4. Fournier JP, *et al.* Coma hypoglycémique chez une patiente traitée par glipizide et fluconazole: une possible interaction? *Therapie* 1992; **47:** 446–7.
5. Abad S, *et al.* Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; **52:** 456–7.
6. Krishnaiah YSR, *et al.* Interaction between tolbutamide and ketoconazole in healthy subjects. *Br J Clin Pharmacol* 1994; **37:** 205–7.
7. Meurice JC, *et al.* Interaction miconazole et sulfamides hypoglycémiants. *Presse Med* 1983; **12:** 1670.

Ciclosporin. For the effect of glibenclamide on blood concentrations of ciclosporin see Hypoglycaemic Drugs, p.1828.

Metformin. Results apparently suggesting increased mortality in patients who received intensive drug therapy with metformin and a sulfonylurea were reported by the UK Prospective Diabetes Study.[1] This was considered to be artefactual, since it was not confirmed by epidemiological analysis, and such combinations are widely used in practice, but some concern remains and further study is needed.

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65. Correction. *ibid.*; 1558.

Thyroid hormones. It has been suggested that starting thyroid replacement therapy may increase the requirement for insulin or oral antidiabetic drugs in diabetic patients, which would not seem unreasonable given the stimulant effects of thyroid hormones on metabolic function. For a discussion of the mooted effects of sulfonylureas on thyroid function, see under Precautions, above.

Pharmacokinetics

◊ Reviews.

1. Marchetti P, Navalesi R. Pharmacokinetic-pharmacodynamic relationships of oral hypoglycaemic agents: an update. *Clin Pharmacokinet* 1989; **16:** 100–28.
2. Marchetti P, *et al.* Pharmacokinetic optimisation of oral hypoglycaemic therapy. *Clin Pharmacokinet* 1991; **21:** 308–17.
3. Harrower AD. Pharmacokinetics of oral antihyperglycaemic agents in patients with renal insufficiency. *Clin Pharmacokinet* 1996; **31:** 111–19.

Uses and Administration

The sulfonylurea antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p.431). They are given to supplement treatment by diet modification when such modification has not proved effective on its own, although metformin is preferred in patients who are obese.

Sulfonylureas appear to have several modes of action, apparently mediated by inhibition of ATP-sensitive potassium channels. Initially, secretion of insulin by functioning islet beta cells is increased. However, insulin secretion subsequently falls again but the hypoglycaemic effect persists and may be due to inhibition of hepatic glucose production and increased sensitivity to any available insulin; this may explain the observed clinical improvement in glycaemic control. The duration of action of sulfonylureas is variable; drugs such as tolbutamide are relatively short-acting (about 6 to 12 hours) while chlorpropamide has a prolonged action (over 24 hours).

Sulfonylurea therapy may be combined with metformin or other oral hypoglycaemics in patients who fail to respond to a single type of drug; such combination therapy is usually tried (in the absence of contraindications) before considering the addition of, or transfer to, insulin therapy.

◊ Reviews.

1. Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 2004; **64:** 1339–58.

Tolazamide *(BAN, USAN, rINN)*

NSC-70762; Tolatsamidi; Tolazamid; Tolazamida; Tolazamidum; U-17835. 1-(Perhydroazepin-1-yl)-3-tosylurea; 1-(Perhydroazepin-1-yl)-3-*p*-tolylsulphonylurea.

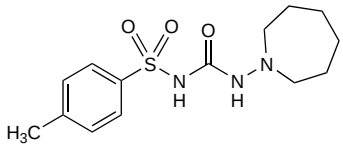
Толазамид

$C_{14}H_{21}N_3O_3S$ = 311.4.

CAS — 1156-19-0.

ATC — A10BB05.

ATC Vet — QA10BB05.



Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2008 (Tolazamide). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

USP 31 (Tolazamide). A white or off-white crystalline powder, odourless or having a slight odour. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460.

Porphyria. Tolazamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for sulfonylureas in general, p.461.

Pharmacokinetics

Tolazamide is slowly absorbed from the gastrointestinal tract, peak plasma concentrations occurring 4 to 8 hours after a dose by mouth, and is extensively bound to plasma proteins. It has a half-life of about 7 hours. It is metabolised in the liver to metabolites with some hypoglycaemic activity. About 85% of an oral dose is excreted in the urine, chiefly as metabolites.

Uses and Administration

Tolazamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) and has a duration of action of at least 10 hours and sometimes up to 20 hours. The usual initial dose is 100 to 250 mg daily given as a single dose with breakfast. Dosage may be increased if necessary at weekly intervals by 100 to 250 mg, usually to a maximum of 1 g daily; no further benefit is likely to be gained with higher doses. Doses of more than 500 mg daily may be given in divided doses.

Preparations

BP 2008: Tolazamide Tablets;
USP 31: Tolazamide Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Tolinase†.

Tolbutamide *(BAN, rINN)*

Butamidum; Tolbutamid; Tolbutamida; Tolbutamidas; Tolbutamidi; Tolbutamidum; Tolglybutamide. 1-Butyl-3-tosylurea; 1-Butyl-3-*p*-tolylsulphonylurea.

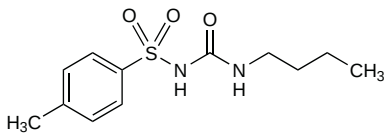
Тольбутамид

$C_{12}H_{18}N_2O_3S$ = 270.3.

CAS — 64-77-7 (tolbutamide); 473-41-6 (tolbutamide sodium).

ATC — A10BB03; V04CA01.

ATC Vet — QA10BB03; QV04CA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Tolbutamide). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Tolbutamide). A white or practically white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol and in chloroform.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460. Tolbutamide was implicated in the controversial reports of excess cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p.461).

Thrombophlebitis with thrombosis has occurred after the intravenous injection of tolbutamide sodium, but this is usually painless and the vein gradually recovers. Rapid injection may cause a transient mild pain or sensation of heat in the vein.

The *BNF* has suggested that tolbutamide may be suitable for use in patients with renal impairment, but that careful monitoring of blood-glucose concentration is essential. UK licensed product information recommends that it should not be used in patients with severe renal impairment.

Breast feeding. Tolbutamide is distributed into breast milk in relatively low quantities.[1] The American Academy of Pediatrics[2] states that, although usually compatible with breast feeding, use of tolbutamide by breast-feeding mothers may possibly result in jaundice in the infant.

1. Moiel RH, Ryan JR. Tolbutamide orinase in human breast milk. *Clin Pediatr (Phila)* 1967; **6:** 480.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/07/04)

Porphyria. Tolbutamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for sulfonylureas in general, p.461.

Pharmacokinetics

Tolbutamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins; the half-life is generally within the range of 4 to 7 hours but may be considerably longer. Tolbutamide is metabolised in the liver by hydroxylation mediated by the cytochrome P450 isoenzyme CYP2C9. It is excreted in the urine chiefly as metabolites with little hypoglycaemic activity. Tolbutamide has been detected in breast milk.

Uses and Administration

Tolbutamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) and has a duration of action of about 10 hours.

The usual initial dose in type 2 diabetes mellitus may range from 1 to 2 g daily, given either as a single dose with breakfast or, more usually, in divided doses. Maintenance doses usually range from 0.25 to 2 g daily. Although it is unlikely that the response will be improved by increasing the dose further, daily doses of 3 g have been given.

Tolbutamide sodium ($C_{12}H_{17}N_2NaO_3S$ = 292.3) has sometimes been used in the diagnosis of insulinoma as well as other pancreatic disorders including diabetes mellitus. The equivalent of 1 g of tolbutamide is given by intravenous injection as a 5% solution usually over 2 to 3 minutes. Tolbutamide sodium 1.08 g is equivalent to about 1 g of tolbutamide.

Diagnosis and testing. References.

1. McMahon MM, *et al.* Diagnostic interpretation of the intravenous tolbutamide test for insulinoma. *Mayo Clin Proc* 1989; **64:** 1481–8.
2. Marks V. Diagnosis and differential diagnosis of hypoglycemia. *Mayo Clin Proc* 1989; **64:** 1558–61.

Preparations

BP 2008: Tolbutamide Tablets;
USP 31: Tolbutamide for Injection; Tolbutamide Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Rastinon; ***Cz.:*** Dirastan; ***Denm.:*** Arcosal; ***Ger.:*** Orabet; ***Hong Kong:*** Diatol; ***Israel:*** Orsinon; ***Mex.:*** Artosin; Bioglusil†; Dabetil; Diatelan; Diaval; Flusan; Ifumelus†; Rastinon; ***NZ:*** Diatol; ***Pol.:*** Diabetol; ***S.Afr.:*** Tydadex; ***Singapore:*** Tolmide; ***USA:*** Orinase; Orinase Diagnostic.

Troglitazone *(BAN, USAN, rINN)*

CI-991; CS-045; GR-92132X; Troglitazona; Troglitazonum. (±)-*all-rac*-5-{*p*-[(6-Hydroxy-2,5,7,8-tetramethyl-2-chromanyl)methoxy]benzyl}-2,4-thiazolidinedione.

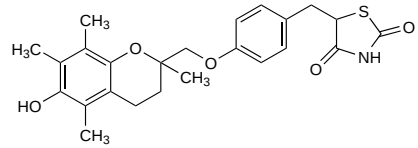
Троглитазон

$C_{24}H_{27}NO_5S$ = 441.5.

CAS — 97322-87-7.

ATC — A10BG01.

ATC Vet — QA10BG01.



Adverse Effects and Precautions

Troglitazone has been associated with severe hepatic reactions, sometimes fatal, which has led to its withdrawal in most countries. Regular monitoring of liver function during therapy, and withdrawal of the drug in any patient who develops jaundice or signs of liver dysfunction, is required. It should not be given to patients with pre-existing moderate or severe elevations of liver enzyme values, or active liver disease. Increased plasma volume has been reported in healthy subjects given troglitazone: it should be used with caution in patients with heart failure. Other adverse effects reported in patients receiving troglitazone include dizziness, headache, fatigue, musculoskeletal pain, and nausea and vomiting. There is no evidence of hypoglycaemia associated with the use of troglitazone alone.

Effects on the liver. The UK CSM[1] was aware of over 130 cases of hepatic reactions to troglitazone worldwide as of December 1997, although only 1 had been in the UK. There had been 6 deaths. The average time to the onset of the reaction was 3 months, but the frequency of these reactions, and the existence of risk factors predisposing to them, were unclear. The manufacturers had voluntarily withdrawn the drug in the UK.

The US manufacturer and the FDA recommended[2] a schedule for routine monitoring of liver function in November 1997 and revised this again in December 1997. It was estimated that 2% of patients treated with troglitazone would have elevated liver enzyme values necessitating discontinuation of the drug. The FDA[3] had received 560 reports of troglitazone-associated hepatotoxicity by June 1998. There were 24 cases of hepatic failure which were likely to have been caused by the drug; 21 patients died and 3 patients received transplants. More intensive liver function monitoring recommendations were made by the US manufacturer again in July 1998 and in June 1999. Subsequently the manufacturer withdrew the drug in Australia, Japan, and the USA in March 2000. The clinical details of 94 cases of liver failure associated with troglitazone, which were reported to the FDA, have been reviewed.[4]

1. CSM/MCA. Troglitazone (Romozin) withdrawn. *Current Problems* 1997; **23:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 02/06/06)
2. Anonymous. Troglitazone and liver injury. *WHO Drug Inf* 1998; **12:** 13.
3. Misbin RI. Troglitazone-associated hepatic failure. *Ann Intern Med* 1999; **130:** 330.
4. Graham DJ, *et al.* Troglitazone-induced liver failure: a case study. *Am J Med* 2003; **114:** 299–306.

Interactions

Troglitazone may enhance the hypoglycaemic effects of sulfonylureas; dosage adjustment may be necessary. There is a possibility that troglitazone may enhance the metabolism of drugs metabolised by cytochrome P450 isoenzyme CYP3A4, including some oral contraceptives and terfenadine.

Ciclosporin. For the effect of troglitazone on blood concentrations of ciclosporin see Hypoglycaemic Drugs, p.1828.

Colestyramine. Colestyramine markedly impaired the absorption of troglitazone.[1]

1. Young MA, *et al.* Concomitant administration of cholestyramine influences the absorption of troglitazone. *Br J Clin Pharmacol* 1998; **45:** 37–40.

Pharmacokinetics

Troglitazone is rapidly absorbed after oral doses, with peak plasma concentrations 1 to 3 hours after a dose. Bioavailability is about 53%; absorption is markedly increased in the presence of food. In the body, troglitazone is more than 99% bound to plasma albumin. It is extensively metabolised in the liver and excreted largely in faeces as metabolites; small amounts of metabolites are excreted in urine. Plasma elimination half-life ranges from 10 to 39 hours.

◊ Reviews.

1. Loi C-M, *et al.* Clinical pharmacokinetics of troglitazone. *Clin Pharmacokinet* 1999; **37:** 91–104.