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.

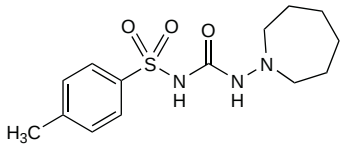
Толазамид

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

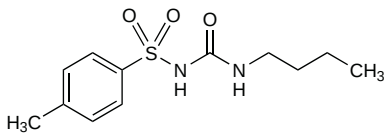
Тольбутамид

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

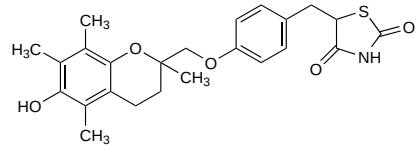
Троглитазон

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

Uses and Administration

Troglitazone is a thiazolidinedione oral antidiabetic (see Rosiglitazone Maleate, p.458). It has been given orally for the treatment of type 2 diabetes mellitus (p.431) although as mentioned above it has been withdrawn in most countries owing to hepatotoxicity.

◊ Reviews.

1. Plosker GL, Faulds D. Troglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 1999; **57:** 409–38.
2. Parulkar AA, *et al.* Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001; **134:** 61–71.

Preparations

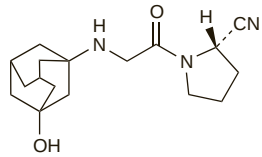
Proprietary Preparations (details are given in Part 3)
Mex.: Rezulin†.

Vildagliptin *(rINN)*

LAF-237; NVP-LAF-237; Vildagliptina; Vildagliptine; Vildagliptinum. (2*S*)-{[(3-Hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile.

Вильдаглиптин

$C_{17}H_{25}N_3O_2$ = 303.4.
CAS — 274901-16-5.
ATC — A10BH02.
ATC Vet — QA10BH02.



Profile

Vildagliptin 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. Vildagliptin is used in the treatment of type 2 diabetes mellitus (p.431); it may be added to metformin, a sulfonylurea, or a thiazolidinedione, when monotherapy with these is insufficient. It is given orally in a dose of 50 mg twice daily when given with metformin or a thiazolidinedione, and in a dose of 50 mg once daily in the morning when given with a sulfonylurea. A total daily dose of more than 100 mg of vildagliptin is not recommended, and in patients taking a combination of vildagliptin with a sulfonylurea, a dose of vildagliptin 100 mg daily is no more effective than vildagliptin 50 mg daily. Vildagliptin may be given with or without food.

Adverse effects of vildagliptin may include dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory-tract infection, and arthralgia. Rare cases of hepatic dysfunction, including hepatitis, have been reported. Vildagliptin should not be used in patients with hepatic impairment; liver function should be tested before starting the drug, and monitored during therapy (every 3 months in the first year and periodically thereafter). Vildagliptin should be stopped if there is a persistent increase of 3 or more times the upper limit of normal in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or if the patient develops jaundice or other signs of liver dysfunction; in such cases, it should not be restarted.

◊ Reviews.

1. Kleppinger EL, Helms K. The role of vildagliptin in the management of type 2 diabetes mellitus. *Ann Pharmacother* 2007; **41:** 824–32.
2. Henness S, Keam SJ. Vildagliptin. *Drugs* 2006; **66:** 1989–2001.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Galvus; ***Fr.:*** Galvus; ***Port.:*** Galvus; ***UK:*** Galvus.

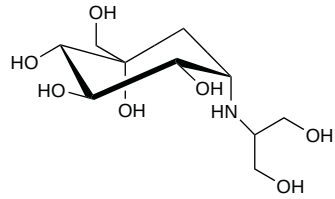
Multi-ingredient: ***Cz.:*** Eucreas; ***Fr.:*** Eucreas; ***UK:*** Eucreas.

Voglibose *(USAN, rINN)*

A-71100; AO-128; Voglibosa; Voglibosum. 3,4-Dideoxy-4-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-2-*C*-(hydroxymethyl)-*D*-epi-inositol.

Воглибоза

$C_{10}H_{21}NO_7$ = 267.3.
CAS — 83480-29-9.
ATC — A10BF03.
ATC Vet — QA10BF03.



Pharmacopoeias. In *Jpn*.

Profile

Voglibose is an alpha-glucosidase inhibitor with general properties similar to those of acarbose (p.436). It is used in the treatment of diabetes mellitus (p.431) in oral doses of 200 to 300 micrograms three times daily before meals.

Hepatic encephalopathy. Voglibose has been investigated[1] in the management of hepatic encephalopathy (p.1697).

1. Uribe M, *et al.* Beneficial effect of carbohydrate maldigestion induced by a disaccharidase inhibitor (AO-128) in the treatment of chronic portal systemic encephalopathy: a double-blind, randomized controlled trial. *Scand J Gastroenterol* 1998; **33:** 1099–1106.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Basen; ***Philipp.:*** Basen; ***Thai.:*** Basen.