### 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It has been given orally for the treatment of type 2 diabetes mellitus (p.431) although as mentioned above it has been withdrawn in most countries owing to hepatotoxicity.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†.

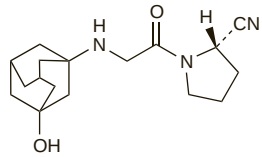
---

## 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.

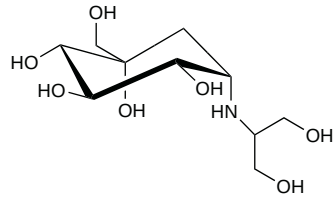
---

## 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.

(negative myoclonus). The term 'myoclonus' is non-specific and classification is important in order to decide on treatment:[1-4]

- physiological (in normal subjects)
- essential (no known cause)
- epileptic (seizures dominate)
- symptomatic (encephalopathy dominates—causes include storage diseases, neurodegenerative syndromes, toxic and drug-induced syndromes, and hypoxia)

In epileptic myoclonus, epileptic seizures (myoclonic seizures in which the motor manifestation is myoclonus) dominate. Their treatment is discussed under Epilepsy, above. Essential myoclonus may benefit from *clonazepam*. *Botulinum toxin* has been used successfully for spasmodic movements in some forms of myoclonus.

Myoclonus may also be subdivided into cortical, reticular, or spinal forms. Cortical myoclonus is considered to be a subset of epilepsy and responds best to antiepileptics, usually *valproate* and/or clonazepam; *piracetam* or *levetiracetam* are also used, usually as adjunctive therapy. Reticular myoclonus is usually caused by anoxia or acute encephalopathy and may be treated with clonazepam; *serotonin* or serotonergic agonists have also been tried. Post-hypoxic myoclonus occurring after hypoxic coma may respond to *oxitriptan* or serotonin combined with *carbidopa*; antiepileptics may help.


1. Caviness JN. Myoclonus. *Mayo Clin Proc*. 1996; **71:** 679–88.
2. Blindauer K. Myoclonus and its disorders. *Neurol Clin North Am* 2001; **19:** 723–34.
3. Agarwal P, Frucht SJ. Myoclonus. *Curr Opin Neurol* 2003; **16:** 515–21.
4. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004; **3:** 598–607.


**Neonatal seizures.** Neonatal seizures differ from epilepsy, and the definitions in the 1989 international classification of epilepsy and epileptic syndromes (see above) may be of little value; (a study[1] has suggested that the proposed 2001 classification may be more helpful). They are frequently subtle and difficult to recognise.[2] Causes include asphyxia, glucose or electrolyte imbalance, infection, CNS or cerebrovascular lesions, inborn errors of metabolism, and drug withdrawal or intoxication.[3-5]

Neonatal seizures represent a neurological emergency in the newborn and rapid diagnosis and treatment is essential.[3-7] Infusion of glucose or electrolytes may be of benefit.[4,5] Current practice involves giving antiepileptic drugs to control seizures, although there is no consensus on, nor good evidence for, their use.[2,7] *Phenobarbital* and *phenytoin* are the most widely used.[3-6] Traditionally, phenobarbital has been considered to be the mainstay of treatment for all types of seizures in neonates; however response rates are variable.[6-8] If seizures persist, phenytoin may be added to therapy.[8] Other drugs that have been tried include *carbamazepine*, *levetiracetam*,[9] *benzodiazepines*,[3-5,8,10,11] *lidocaine*,[3,8,10] and *primidone*.[4,5] Pyridoxine-dependent seizures can be abolished by regular large doses of the vitamin[4,5] (see p.1979).


1. Mastrangelo M, *et al.* Epileptic seizures, epilepsy and epileptic syndromes in newborns: a nosological approach to 94 new cases by the 2001 proposed diagnostic scheme for people with epileptic seizures and with epilepsy. *Seizure* 2005; **14:** 304–11.
2. Rennie J, Boylan G. Treatment of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F148–F150.
3. Evans D, Levene M. Neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F70–F75.
4. Hill A. Neonatal seizures. *Pediatr Rev* 2000; **21:** 117–21.
5. Painter MJ, Alvin J. Neonatal seizures. *Curr Treat Options Neurol* 2001; **3:** 237–48.
6. Painter MJ, *et al.* Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999; **341:** 485–9.
7. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 09/06/08).
8. Boylan GB, *et al.* Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology* 2004; **62:** 486–8.
9. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.
10. Shany E, *et al.* Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007; **22:** 255–9.
11. Castro Conde JR, *et al.* Midazolam in neonatal seizures with no response to phenobarbital. *Neurology* 2005; **64:** 876–9.


**Porphyria.** Convulsions may occur at the peak of an attack of acute porphyria (p.1448) but usually disappear as the attack resolves and therapy should be aimed at the underlying disease. However, some patients continue to have convulsions while in remission and their management poses a major therapeutic problem as all the first-line antiepileptics have been associated with acute attacks.[1,2] Barbiturates (*phenobarbital*, *primidone*), hydantoins *(phenytoin, ethotoin)*, and *carbamazepine* are considered unsafe, as is *sultiame*. There is limited evidence that the *benzodiazepines, sodium valproate*, and probably *valpromide* are porphyrinogenic but status epilepticus has been treated successfully with intravenous *diazepam*. Seizure prophylaxis may be undertaken as a calculated risk using valproate or *clonazepam* if considered essential. *Magnesium sulfate* is safe. *Clomethiazole* is also probably safe. *Gabapentin* and *vigabatrin* have each been tried in a few patients without ill-effect, although there has been a report of a bullous skin eruption in a patient with porphyria cutanea tarda given vigabatrin.[3] Of the other newer antiepileptics, *oxcarbazepine* was used successfully in one patient whilst *lamotrigine* was associated with an acute porphyric attack in another; *tiagabine* and *topiramate* have been found to increase hepatic and urinary porphobilinogen concentrations.[2] Other antiepileptics such as the succinimides *(ethosuximide, mesuximide, phensuximide)* and oxazolidinediones *(trimethadione)* are considered to be unsafe.

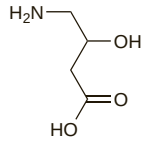

1. Gorchein A. Drug treatment in acute porphyria. *Br J Clin Pharmacol* 1997; **44:** 427–34.
2. Solinas C, Vajda FJ. Epilepsy and porphyria: new perspectives. *J Clin Neurosci* 2004; **11:** 356–61.
3. Hommel L, *et al.* Acute bullous skin eruption after treatment with vigabatrine. *Dermatology* 1995; **191:** 181.


## 4-Amino-3-hydroxybutyric Acid

Ácido 4-amino-3-hidroxibutírico; γ-Amino-β-hydroxybutyric acid; Buxamin; Gabob; Gamma-amino-beta-hydroxybutyric acid.

4-Амино-3-оксимасляная Кислота

$C_4H_9NO_3$ = 119.1.
*CAS — 352-21-6.*



### Profile

Aminohydroxybutyric acid has been claimed to be of value in a variety of neurological disorders including use as an adjunct in the treatment of epilepsy. It has also been promoted as a dietary supplement for its supposed beneficial effects on the CNS and growth hormone. It should be distinguished from its isomer 3-amino-4-hydroxybutyric acid (GOBAB), which is reported to possess anti-inflammatory and antifungal activity.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Gabimex; ***Braz.:*** Gamibetal†; ***Ital.:*** Gamibetal; ***Mex.:*** Gamibetal; ***Port.:*** Gabomade; Gamibetal†.

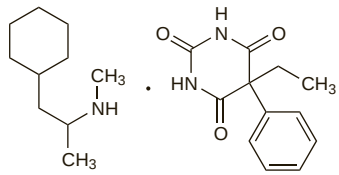
**Multi-ingredient:** ***Arg.:*** Gabimex Plus; ***Braz.:*** Gamibetal Complex†; ***Ital.:*** Gamibetal Complex; Gamibetal Plus; Parvisedil; ***Mex.:*** Gamibetal Complex; ***Port.:*** Gabisedil†; Gamibetal Compositum†; ***Spain:*** Cefabol; Dorken; Gamalate B6; Redutona.

## Barbexaclone *(rINN)*

Barbeksaklon; Barbexaclona; Barbexaclonum. Compound of (–)-*N*,α-Dimethylcyclohexaneethylamine with 5-ethyl-5-phenylbarbituric acid .

Барбексаклон

$C_{12}H_{12}N_2O_3$,$C_{10}H_{21}N$ = 387.5.
*CAS — 4388-82-3.*
*ATC — N03AA04.*
*ATC Vet — QN03AA04.*



### Profile

Barbexaclone is a compound of levopropylhexedrine (see under Propylhexedrine, p.2163) with phenobarbital (p.492). It is used in the treatment of various types of epilepsy (p.465). Usual adult doses are 200 to 400 mg daily given by mouth in divided doses.

### Preparations

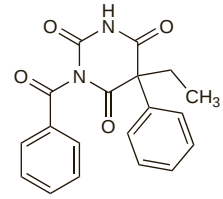
**Proprietary Preparations** (details are given in Part 3)
***Austria:*** Maliasin; ***Braz.:*** Maliasin; ***Gr.:*** Maliasin; ***Ital.:*** Maliasin; ***Switz.:*** Maliasin; ***Turk.:*** Maliasin.

## Benzobarbital *(rINN)*

Benzobarbitalum; Benzobarbitone; Benzonal; Benzonalum. 1-Benzoyl-5-ethyl-5-phenylbarbituric acid.

Бензобарбитал

$C_{19}H_{16}N_2O_4$ = 336.3.
*CAS — 744-80-9.*



NOTE. The name benzonal has also been used as a proprietary name for benzonatate (p.1552).

**Pharmacopoeias.** In *Int.*

### Profile

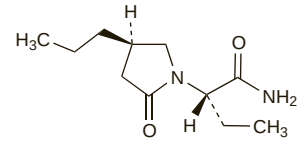
Benzobarbital is a barbiturate used in the treatment of epilepsy.

## Brivaracetam *(USAN, rINN)*

Brivaracétam; Brivaracetamum; UCB-34714. (2*S*)-2-[(4*R*)-2-Oxo-4-propylpyrrolidin-1-yl]butanamide.

Бриварацетам

$C_{11}H_{20}N_2O_2$ = 212.3.
*CAS — 357336-20-0.*



### Profile

Brivaracetam is under investigation for the treatment of various types of epilepsy including progressive myoclonic epilepsy and refractory partial seizures.

◊ References.

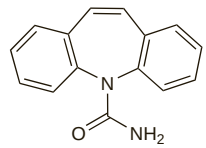

1. Sargentini-Maier ML, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. *Br J Clin Pharmacol* 2007; **63:** 680–8.
2. Rolan P, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men. *Br J Clin Pharmacol* 2008; **66:** 71–5.
3. Malawska B, Kulig K. Brivaracetam: a new drug in development for epilepsy and neuropathic pain. *Expert Opin Invest Drugs* 2008; **17:** 361–9.


# Carbamazepine *(BAN, USAN, rINN)*

Carbamazepina; Carbamazépine; Carbamazepinum; G-32883; Karbamatsepiini; Karbamazepin; Karbamazepinas; Karbamazepinum. 5*H*-Dibenz[*b,f*]azepine-5-carboxamide.

Карбамазепин

$C_{15}H_{12}N_2O$ = 236.3.
*CAS — 298-46-4.*
*ATC — N03AF01.*
*ATC Vet — QN03AF01.*



**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
**Ph. Eur. 6.2** (Carbamazepine). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers.
**USP 31** (Carbamazepine). A white or off-white powder. Practically insoluble in water; soluble in alcohol and in acetone. Store in airtight containers.

**Incompatibility.** Carbamazepine suspension should be mixed with an equal volume of diluent before nasogastric use as undiluted suspension is adsorbed onto PVC nasogastric tubes.[1]