the standard preparation. For doses used in children and adolescents, see below.

Metformin is also used as the chlorophenoxyacetate and as the embonate.

◊ General references.

1. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; **49:** 721–49.
2. Anonymous. Metformin for non-insulin-dependent diabetes mellitus. *Med Lett Drugs Ther* 1995; **37:** 41–2.
3. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; **334:** 574–9.
4. Melchior WR, Jaber LA. Metformin: an antihyperglycemic agent for treatment of type II diabetes. *Ann Pharmacother* 1996; **30:** 158–64.
5. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997; **102:** 99–110.
6. Klepser TB, Kelly MW. Metformin hydrochloride: an antihyperglycemic agent. *Am J Health-Syst Pharm* 1997; **54:** 893–903. Correction. *ibid.*; 1335.
7. Kirpichnikov D, *et al.* Metformin: an update. *Ann Intern Med* 2002; **137:** 25–33.
8. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs* 2003; **63:** 1879–94.

Action. A review of the action of metformin[1] considered that although a number of possible mechanisms have been suggested (see Uses and Administration of Biguanide Antidiabetics, p.438), the major action of metformin lay in increasing glucose transport across the cell membrane in skeletal muscle. There is also some evidence *in vitro* that it can inhibit the formation of advanced glycosylation end-products.[2]

1. Klip A, Leiter LA. Cellular mechanism of action of metformin. *Diabetes Care* 1990; **13:** 696–704.
2. Tanaka Y, *et al.* Inhibitory effect of metformin on formation of advanced glycation end products. *Curr Ther Res* 1997; **58:** 693–7.

Administration in children. In children aged 10 years and older with type 2 diabetes mellitus, oral metformin hydrochloride may be used in a starting dose of 500 mg or 850 mg once daily, or 500 mg twice daily, given with or after a meal. It may be gradually increased if needed, at intervals of at least 1 week, to a maximum of 2 g daily given in 2 or 3 divided doses. Modified-release preparations are generally not licensed for use in children.

Although rare, the incidence of type 2 diabetes is increasing in children and adolescents, related in part to the increase in obesity occurring particularly in westernised countries. A small placebo-controlled study[1] of patients aged 10 to 17 years with type 2 diabetes found that metformin improved glycaemic control and that adverse effects were similar to those in adults. In obese children and adolescents with hyperinsulinaemia, who are at risk of developing type 2 diabetes, small studies[2,3] of metformin use have reported improvements in body composition and fasting insulin concentrations. There has also been some interest in the use of metformin as an adjunct to insulin in adolescents with type 1 diabetes; improvements in glycaemic control[4,5] and reductions in insulin doses[4] have been reported.

1. Jones KL, *et al.* Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2002; **25:** 89–94.
2. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Abstract: *Pediatrics* 2001; **107:** 763–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/4/e55 (accessed 25/06/07)
3. Srinivasan S, *et al.* Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. *J Clin Endocrinol Metab* 2006; **91:** 2074–80.
4. Hamilton J, *et al.* Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care* 2003; **26:** 138–43.
5. Särnblad S, *et al.* Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity. *Eur J Endocrinol* 2003; **149:** 323–9.

Diabetes mellitus. Results of the United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive blood glucose control with metformin reduces the risk of diabetic complications and death in overweight patients with type 2 diabetes.[1] The study also generated some concern regarding intensive therapy with metformin plus a sulfonylurea (see under Interactions, p.462) but this was not borne out on further analysis and such combinations are widely used. Metformin is also used with the thiazolidinediones,[2-5] or with insulin[6] in patients requiring combined or more intensive therapy. Metformin has also been investigated for the prevention of type 2 diabetes in patients at high risk. Although metformin treatment for an average 2.8 years reduced the incidence of type 2 diabetes by 31% in a study[7] of patients with impaired glucose tolerance, intensive lifestyle modification was actually more effective (58% reduction). Lifestyle modification was also more effective than metformin in reducing cardiovascular risk factors[8] and the development of the metabolic syndrome.[9] The durability of these effects is unknown but follow-up of this study is ongoing.

There is some interest in using oral hypoglycaemics as adjuncts to insulin therapy in patients with type 1 diabetes. Short-term results from small studies have suggested that metformin may be beneficial, in this context, in adolescents with pubertal insulin resistance (see also Administration in Children, above) and perhaps in adults who are overweight or otherwise at risk of reduced insulin sensitivity.[10]

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.
2. Fonseca V, *et al.* Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000; **283:** 1695–1702. Correction. *ibid.*; **284:** 1384.
3. Einhorn D, *et al.* Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther* 2000; **22:** 1395–1409.
4. Wellington K. Rosiglitazone/metformin. *Drugs* 2005; **65:** 1581–92.
5. Deeks ED, Scott LJ. Pioglitazone/metformin. *Drugs* 2006; **66:** 1863–77.
6. Avilés-Santa L, *et al.* Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; **131:** 182–88.
7. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.
8. The Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. *Diabetes Care* 2005; **28:** 888–94.
9. Orchard TJ, *et al.* The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005; **142:** 611–19.
10. Jefferies CA, *et al.* Potential adjunctive therapies in adolescents with type 1 diabetes mellitus. *Treat Endocrinol* 2004; **3:** 337–43.

Polycystic ovary syndrome. It has been suggested that hyperinsulinism may play a pathogenetic role in stimulating the abnormal androgen production from the ovary seen in women with polycystic ovary syndrome (PCOS, p.2080). Most early studies of metformin in PCOS were small, observational, and of short duration, with mixed results. Although there were reports of reduced insulin levels, increased insulin sensitivity, and improved androgen concentrations, other studies failed to confirm these effects.[1] Later randomised studies were also small, but some were of longer duration. These reported weight reductions of obese patients,[2] reductions in insulin levels[2-4] and increased sensitivity,[5] improved androgen and other hormonal measures,[2,3,5] improved menstrual patterns,[2,4,5] and reduced hirsutism,[2] but again, not consistently. Metformin has also been reported to increase the rate of spontaneous ovulation,[6,7] and may improve the outcome of IVF procedures.[8] Combination of metformin with clomifene appeared to improve ovulatory response, compared with clomifene alone, in studies of women with PCOS,[6,9] though there is also a report of no apparent benefit.[10] Furthermore, 2 large, placebo-controlled studies have found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[11,12]

Some consider that current evidence supports a trial of metformin in patients with anovulation, androgen excess, and vascular risk factors, but because of the lack of data on long-term safety such use should be supervised by an endocrinologist or a physician with suitable expertise.[1]

1. Norman RJ, *et al.* Metformin and intervention in polycystic ovary syndrome. *Med J Aust* 2001; **174:** 580–3.
2. Pasquali R, *et al.* Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000; **85:** 2767–74.
3. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17α activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 1996; **335:** 617–23.
4. Morin-Papunen LC, *et al.* Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab* 2000; **85:** 3161–8.
5. Moghetti P, *et al.* Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000; **85:** 139–46.
6. Nestler JE, *et al.* Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998; **338:** 1876–80.
7. Fleming R, *et al.* Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab* 2002; **87:** 569–74.
8. Stadtmauer LA, *et al.* Metformin treatment of patients with polycystic ovary syndrome undergoing in vitro fertilization improves outcomes and is associated with modulation of the insulin-like growth factors. *Fertil Steril* 2001; **75:** 505–9.
9. Kocak M, *et al.* Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. *Fertil Steril* 2002; **77:** 101–6.
10. Sturrock NDC, *et al.* Metformin does not enhance ovulation induction in clomiphene resistant polycystic ovary syndrome in clinical practice. *Br J Clin Pharmacol* 2002; **53:** 469–73.
11. Moll E, *et al.* Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. Abridged version: *BMJ* 2006; **332:** 1485–8. Full version: http://www.bmj.com/cgi/reprint/332/7556/1485 (accessed 17/06/08) Correction available at: http://www.bmj.com/cgi/content/full/336/7643/0-b (accessed 17/06/08)
12. Legro RS, *et al.* Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007; **356:** 551–66.

Preparations

BP 2008: Metformin Tablets;
USP 31: Glipizide and Metformin Hydrochloride Tablets; Glyburide and Metformin Hydrochloride Tablets; Metformin Hydrochloride Extended-Release Tablets; Metformin Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Baligluc; DBI AP; Diab Dos; Glucaminol; Glucogood; Glucophage; Isl-otin; Mectin; Medobis; Metforal; Metfori†; Oxemet; Reduglucl; ***Austral.:*** Diabex; Diaformin; Glucohexal; Glucomet; Glucophage; Novomet; ***Austria:*** Clonarol; Desugar; Diabetex; Glucomin; Glucophage; Meglucon; Orabet†; ***Belg.:*** Glucophage; Metformax; ***Braz.:*** Diaformin; Dimefor; Formet†; Formyn; Glicefor; Glifage; Glucoformin; Metfordin†; Metformed; Teutoformin; ***Canad.:*** Glucophage; Glumetza; Glycon†; ***Chile:*** Diaglitab; Fintaxim; Glaformil; Glicenex; Glidanil; Glifortex; Glucophage; Hipoglucin; Menarini-Metforal†; ***Cz.:*** Adimet; Diaphage; Glucomerck; Glucophage; Gluformin; Glumetsan; Langerin; Metfirex; Metfogamma; Siofor; Stadamet; ***Denm.:*** Glucophage; Orabet; ***Fin.:*** Diformin; Glucophage; Metforem; Oramet; ***Fr.:*** Diabamyl†; Glucophage; Stagid; ***Ger.:*** Biocos; Diabesin; Diabetase†; espaformin†; Glucobon; Glucophage; Juformin; Mediabet; Meglucon; Mescorit; Met; Metfodoc; Metfogamma; Metfor†; Metform†; MetSurrir; Siofor; Thiabet; ***Gr.:*** Glucofree; Glucophage; Metforil; Sukontrol; ***Hong Kong:*** CP-Metform; Diabetmin; Diaformin; Glucomet; Glucophage; Glumet; Guamet; Melbin; ***Hung.:*** Adimet; Gluformin; Maformin†; Meforal; Meglucon; Merckformin; Metfogamma; Metrivin†; Stadamet; ***India:*** Bigomet†; Emfor; Emnorm; Exermet; Formin†; Glumet; Glyciphage; Glyree M; Insumet; Metlong; Walaphage; X-Met; ***Indon.:*** Benofomin; Diabex; Eraphage; Forbetes; Formell; Gliformin; Glucofor; Glucophage; Glucotika; Gludepatic; Glufor; Glumin; Gradiab; Methormyl; Methpica; Metphar; Reglus; Tudiab; Zumamet; ***Irl.:*** Glucophage; ***Israel:*** Apophage; Glucomin; Glucophage; Glufor; ***Ital.:*** Glucophage; Metbay; Metfonorm; Metforal; Metiguanide; ***Jpn:*** Glycoran; Melbin; ***Malaysia:*** Diabemet†; Diabetmin; Glucomet; Glucophage; Glumet; Riomet; Xmet; ***Mex.:*** Aglumet; Anglucid; Apozemia; Dabex; Debeone; Dimefor; Dinamel; Ficonax; Forlucyl; Glucophage; Glunovag; Harbamind; Ifor; Meglubet; Melbexa; Mifelar; Pharmafet; Pre-Dial; ***Neth.:*** Diabex; Dianorm†; Finormet†; Glucophage; Glumeff; Nifornina; ***Norw.:*** Glucophage; ***NZ:*** Glucomet; Glucophage†; Metomin; ***Philipp.:*** Diafat; Diazen; Euform; Fornidd; Glucare; Glucoform; Glucomed; Glucophage; Glumet; Glyformin; Horsulin; Humamet; I-Max; Insunex; Neoform; Nidcor; Sucranorm; Vimetrol; Xmet; ***Pol.:*** Glucophage†; Gluformin; Metfogamma; Metformax; Metifor; Siofor; ***Port.:*** Diabex; Glucophage; Mekoll; Risidon; Stagid; ***Rus.:*** Bagomet (Багомет); Formin (Формин Плив); Gliformin (Глиформин); Glucophage (Глюкофаж); Metfogamma (Метфогамма); Siofor (Сиофор); ***S.Afr.:*** Glucophage; Metforal; ***Singapore:*** Diabetmin; Diamin†; Glucophage; Glycomet; Glycoran†; Metforal; ***Spain:*** Dianben; ***Swed.:*** Glucophage; ***Switz.:*** Gluconormine; Glucophage; Metfin; ***Thai.:*** Ammiformin; Deson; Diamet; Formin; Gluco; Glucoles-500; Glucolyte; Glucomet†; Glucono; Glucophage; Gluformin; Glustress†; Glutabloc; Gluzolyte; Macromin†; Maformin; ME-F†; Meformed; Metfor; Metfron; Miformin; Pocophage; Poli-Formin; Prophage; Serformin; Siamformet; ***Turk.:*** Glifor; Glucophage; Gluformin; Glukofen; ***UAE:*** Dialon; ***UK:*** Glucophage; Metsol; ***USA:*** Fortamet; Glucophage; Glumetza; Riomet; ***Venez.:*** Diaformina; Dimefor†; Glaformil; Glucaminol; Glucofage.

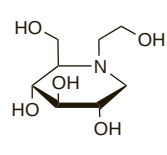
Multi-ingredient: ***Arg.:*** Avandamet; DBI Duo; Glucovance; Gludex Plus; Isloglib; Medobis G; Metformin Duo; Rosiglit-Met; ***Austral.:*** Avandamet; Glucovance; ***Belg.:*** Avandamet; Glucovance; ***Braz.:*** Glucovance; Starform; ***Canad.:*** Avandamet; ***Chile:*** Avandamet; Bi-Euglucon M; Diaglitab Plus; Glifortex-G; Glimet; Glucovance; Glukaut; Hipoglucin DA; ***Cz.:*** Avandamet; Competact; Eucreas; Glibomet; Glubrava; Glucovance; ***Denm.:*** Avandamet; ***Fin.:*** Avandamet; ***Fr.:*** Avandamet; Competact; Eucreas; Glucovance; ***Ger.:*** Avandamet; ***Gr.:*** Avandamet; Normell; ***Hong Kong:*** Avandamet; Glucovance; ***Hung.:*** Avandamet; ***India:*** Betaglim M†; Diaforte; Diaglip M; Exermet GM; Exermet GZ; Exermet P; Gliclamet; Glimiprex MF; Glimulin-MF†; Glinil M; Glizid-M; Glycigon-M; Glycinorm M; Glygard M; Metaglez; P-Glitz M; Piomed M; Piosafe MF; Roglin-M; Rosicon MF; ***Indon.:*** Avandamet; Glucovance; ***Irl.:*** Avandamet; ***Israel:*** Avandamet; ***Ital.:*** Avandamet; Bi-Euglucon M; Glibomet; Gliconorm; Glicorest; Glucomide; Pleiamide; Suguan M; ***Malaysia:*** Avandamet; Glucovance; ***Mex.:*** Apometglu; Avandamet; Bi-Dizalon; Bi-Euglucon M; Bi-Pradia; Duo-Anglucid; Glimetal; Glucotec; Glucovance; Imalet; Insogen Plus; Insusym-Forte; Maviglin; Mellitron; Midapharma; Mifelar-C; Nadib-M; Norfaben M; Obinese; Sibet-C; Sil-Norboral; Wadil; ***Neth.:*** Avandamet; Glucovance; ***Norw.:*** Avandamet; ***Philipp.:*** Avandamet; Euglo Plus; Glucovance; ***Pol.:*** Avandamet; ***Port.:*** Avandamet; Competact; Glucovance; ***Rus.:*** Glibomet (Глибомет); Glucovance (Глюкован); ***S.Afr.:*** Glucovance; ***Singapore:*** Avandamet; Glucovance; ***Spain:*** Avandamet; ***Swed.:*** Avandamet; ***Switz.:*** Avandamet; Diabiformine; Glucovance; ***Thai.:*** Avandamet; ***UK:*** Avandamet; Competact; Eucreas; ***USA:*** Actoplus Met; Avandamet; Diofen; Glucovance; Glybofen; Janumet; Metaglip; ***Venez.:*** Avandamet; Bi-Euglucon; Diaformina Plus; Glucovance; Starform.

Miglitol *(BAN, USAN, pINN)*

Bay-m-1099; Miglitoli; Miglitolum. (2*R*,3*R*,4*R*,5*S*)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol.

Миглитол

$C_8H_{17}NO_5$ = 207.2.
CAS — 72432-03-2.
ATC — A10BF02.
ATC Vet — QA10BF02.



Adverse Effects and Precautions
As for alpha-glucosidase inhibitors in general (see Acarbose, p.436). Skin rash may occur. Miglitol should be used with caution in patients with renal impairment.

Interactions
As for alpha-glucosidase inhibitors in general (see Acarbose, p.436). Miglitol may reduce the bioavailability of propranolol and ranitidine.

Pharmacokinetics
Miglitol is completely absorbed at a dose of 25 mg, but only 50 to 70% is absorbed at a dose of 100 mg. It is not metabolised, and is excreted unchanged in the urine with a plasma elimination half-life of about 2 hours.

Uses and Administration
Miglitol is an alpha-glucosidase inhibitor similar in action to acarbose (p.436). It is given orally in the management of type 2 diabetes mellitus (p.431), alone or with a sulfonylurea. Usual initial doses are 25 mg three times daily with meals, increased if necessary to a maximum of 100 mg three times daily.

◊ References.

1. Campbell LK, *et al.* Miglitol: assessment of its role in the treatment of patients with diabetes mellitus. *Ann Pharmacother* 2000; **34:** 1291–1301.
2. Scott LJ, Spencer CM. Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. *Drugs* 2000; **59:** 521–49.
3. Standl E, *et al.* Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pract* 2001; **51:** 205–13.
4. Chiasson JL, *et al.* The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care* 2001; **24:** 989–94.
5. Van Gaal L, *et al.* Miglitol combined with metformin improves glycaemic control in type 2 diabetes. *Diabetes Obes Metab* 2001; **3:** 326–31.
6. Drent ML, *et al.* Dose-dependent efficacy of miglitol, an alpha-glucosidase inhibitor, in type 2 diabetic patients on diet alone: results of a 24-week double-blind placebo-controlled study. *Diabetes Nutr Metab* 2002; **15:** 152–9.

Preparations
Proprietary Preparations (details are given in Part 3)

Austria: Diastabol; ***Cz.:*** Diastabol; ***Fr.:*** Diastabol; ***Ger.:*** Diastabol; ***Hung.:*** Diastabol; ***India:*** Diamig; Mignar†; ***Mex.:*** Diastabol; ***Neth.:*** Diastabol; ***Pol.:*** Diastabol; ***Port.:*** Diastabol; Limarcan; ***Spain:*** Diastabol; Plumarol; ***Swed.:*** Diastabol†; ***Switz.:*** Diastabol; ***USA:*** Glyset.

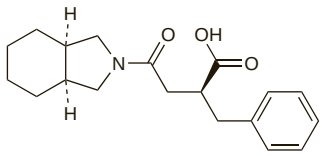
Mitiglinide *(rINN)*

Mitiglinida; Mitiglinidum. (–)-(2*S*,3a,7a-*cis*)-α-Benzylhexahydro-γ-oxo-2-isoindolinebutyric acid.

Митиглинид

$C_{19}H_{25}NO_3$ = 315.4.

CAS — 145375-43-5 (mitiglinide); 145525-41-3 (anhydrous mitiglinide calcium); 207844-01-7 (mitiglinide calcium dihydrate).



Profile
Mitiglinide is a meglitinide antidiabetic that is under investigation in the treatment of type 2 diabetes mellitus.

◊ References.

1. Yoshihara T, *et al.* Therapeutic efficacy of mitiglinide combined with once daily insulin glargine after switching from multiple daily insulin regimen of aspart insulin and glargine in patients with type 2 diabetes mellitus. *Endocr J* 2006; **53:** 67–72.

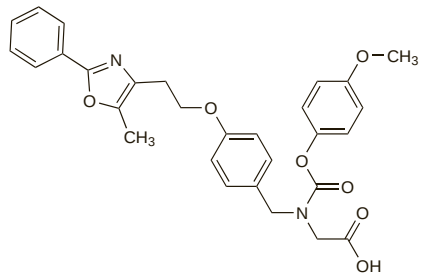
Muraglitazar *(USAN, rINN)*

BMS-298585; Muraglitazarum. {[(4-Methoxyphenoxy)carbonyl]{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}amino}acetic acid.

Мураглитазар

$C_{29}H_{28}N_2O_7$ = 516.5.

CAS — 331741-94-7.



Profile
Muraglitazar is a dual alfa/gamma peroxisome proliferator-activated receptor (PPAR) activator. It has been investigated in the treatment of type 2 diabetes mellitus.

Adverse effects. A review of data from 5 studies suggested that muraglitazar may be associated with an increased risk of adverse cardiovascular events and heart failure.[1]

1. Nissen SE, *et al.* Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005; **294:** 2581–6.

Nateglinide *(USAN, rINN)*

A-4166; AY-4166; DJN-608; Nateglinid; Nateglinida; Natéglinide; Nateglinidi; Nateglinidum; SDZ-DJN-608; Senaglinide; YM-026. (–)-*N*-[(*trans*-4-Isopropylcyclohexyl)carbonyl]-D-phenylalanine.

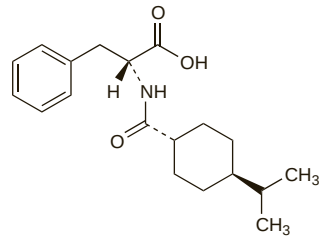
Нателинид

$C_{19}H_{27}NO_3$ = 317.4.

CAS — 105816-04-4.

ATC — A10BX03.

ATC Vet — QA10BX03.



Adverse Effects and Precautions
As for Repaglinide, p.457.

Overdosage. A blood-glucose concentration of 2.0 mmol/litre was measured 1 hour after ingestion of nateglinide 3.42 g in a 30-year-old woman.[1] She was able to walk unaided, but seemed drowsy. The hypoglycaemic effect of nateglinide lasted for 6 hours and was treated with intravenous glucose (total dose 100 g).

1. Nakayama S, *et al.* Hypoglycemia following a nateglinide overdose in a suicide attempt. *Diabetes Care* 2005; **28:** 227–8.

Renal impairment. A single-dose pharmacokinetic study[1] found that moderate to severe renal impairment (creatinine clearance 15 to 50 mL/minute per 1.73 m^2) and haemodialysis did not significantly affect the pharmacokinetics of nateglinide. However, the metabolite M1 has been found to accumulate in patients with renal impairment requiring haemodialysis after repeated doses of nateglinide, but it may be removed by haemodialysis.[2] M1 is a major metabolite that has modest hypoglycaemic activity compared with nateglinide. An analysis[3] of pooled study data found that efficacy and tolerability of nateglinide in elderly diabetic patients were not significantly affected by renal impairment (mean creatinine clearance 50.9 mL/minute per 1.73 m^2). Nevertheless, a 56-year-old diabetic woman whose renal failure was managed with haemodialysis experienced severe hypoglycaemia with nateglinide; the reaction was attributed to the accumulation of M1.[4] Licensed product information in the UK and USA suggest that no dosage adjustment is necessary in renal impairment, although UK information suggests that dose adjustment might be required in patients on haemodialysis.

1. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
2. Inoue T, *et al.* Pharmacokinetics of nateglinide and its metabolites in subjects with type 2 diabetes mellitus and renal failure. *Clin Nephrol* 2003; **60:** 90–5.
3. Del Prato S, *et al.* Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care* 2003; **26:** 2075–80.
4. Nagai T, *et al.* Hypoglycemia due to nateglinide administration in diabetic patient with chronic renal failure. *Diabetes Res Clin Pract* 2003; **59:** 191–4.

Interactions
As with other oral antidiabetics, the efficacy of nateglinide may be affected by drugs independently increasing or decreasing blood glucose concentrations (see Sulfonylureas, p.461).

◊ Reviews.

1. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. In a study[1] of healthy subjects, *rifampicin* reduced the plasma concentrations and half-life of nateglinide, probably by induction of its metabolism by the cytochrome P450 isoenzyme CYP2C9. The glucose-lowering effect of nateglinide was not affected, but there was a marked interindividual variation in the pharmacokinetic changes, and the authors suggested that some diabetic patients could be affected.

1. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of nateglinide in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 427–32.

Antifungals. In a study[1] of healthy subjects, *fluconazole* raised the plasma concentrations and prolonged the half-life of nateglinide, probably by inhibition of its metabolism by the cytochrome P450 isoenzyme CYP2C9. The glucose-lowering effect of nateglinide was not affected, but a low dose of nateglinide had been used and the authors suggested that in diabetic patients fluconazole may enhance and prolong the effects of nateglinide.

1. Niemi M, *et al.* Effect of fluconazole on the pharmacokinetics and pharmacodynamics of nateglinide. *Clin Pharmacol Ther* 2003; **74:** 25–31.

Lipid regulating drugs. A study[1] investigating the effects of the *gemfibrozil* and *itraconazole* combination on the pharmacokinetics of nateglinide showed only a limited interaction. Nateglinide plasma concentrations were raised moderately and the blood glucose response to nateglinide was not significantly changed. This is in contrast to the substantial interaction of gemfibrozil with repaglinide (p.458).

1. Niemi M, *et al.* Coadministration of gemfibrozil and itraconazole has only a minor effect on the pharmacokinetics of the CYP2C9 and CYP3A4 substrate nateglinide. *Br J Clin Pharmacol* 2005; **60:** 208–17.

Pharmacokinetics
Nateglinide is rapidly absorbed after oral doses, with peak plasma concentrations occurring within one hour and an absolute bioavailability of 73%. Nateglinide is 98% bound to plasma proteins. It is mainly metabolised by cytochrome P450 isoenzyme CYP2C9, and to a lesser extent by CYP3A4. Major metabolites include M1 which is less potent than nateglinide. The parent drug and metabolites are mainly excreted in the urine but about 10% is eliminated in the faeces. The elimination half-life is about 1.5 hours.

◊ References.

1. Choudhury S, *et al.* Single-dose pharmacokinetics of nateglinide in subjects with hepatic cirrhosis. *J Clin Pharmacol* 2000; **40:** 634–40.
2. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
3. McLeod JF. Clinical pharmacokinetics of nateglinide: a rapidly-absorbed, short-acting insulinotropic agent. *Clin Pharmacokinet* 2004; **43:** 97–120.

Uses and Administration
Nateglinide, like repaglinide (p.458), is a meglitinide antidiabetic used in the treatment of type 2 diabetes mellitus (p.431). It is given within the 30 minutes before meals in oral doses of 60 or 120 mg three times daily. This may be increased to 180 mg three times daily if necessary. Nateglinide is also given in similar doses with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by these drugs alone.

Although dose adjustment is not generally required in renal impairment, hypoglycaemia has been attributed to accumulation of the metabolite M1 (see above).

◊ References.

1. Dunn CJ, Faulds D. Nateglinide. *Drugs* 2000; **60:** 607–15.
2. Hanefeld M, *et al.* Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 2000; **23:** 202–7.
3. Horton ES, *et al.* Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 2000; **23:** 1660–5.