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.

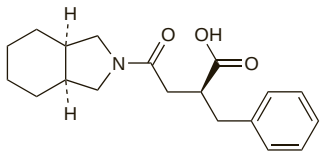
Mitiglinide *(rINN)*

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.

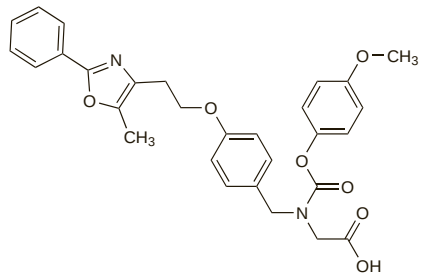
Muraglitazar *(USAN, rINN)*

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.

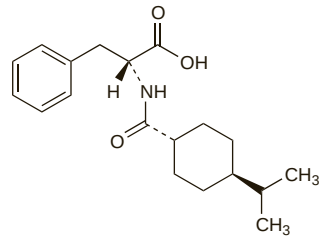
Нателинид

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