New drugs

Alogliptin

Approved indication: type 2 diabetes
Nesina (Takeda)
6.25 mg, 12.5 mg and 25 mg tablets
Australian Medicines Handbook section 10.1.3

Alogliptin is the fifth dipeptidyl peptidase 4 (DPP4) inhibitor to be approved for diabetes in Australia, along with linagliptin (Aust Prescr 2012;35:70-1), saxagliptin (Aust Prescr 2011;34:89-91), vildagliptin (Aust Prescr 2010;33:89-95) and sitagliptin (Aust Prescr 2008;31:49-55).

DPP4 enzymes inactivate incretin hormones which are produced after a meal. These hormones promote insulin release and lower glucagon production which leads to lower serum glucose concentrations. By inhibiting DPP4 enzymes, the 'gliptins' prolong the effects of incretins and improve glycaemic control (Aust Prescr 2008;31:102-4 and 104-8).

Alogliptin's bioavailability is 100%. Following oral administration, peak plasma concentrations are reached after 1–2 hours. The drug is not extensively metabolised and clinically relevant pharmacokinetic drug interactions are not expected. Alogliptin has a terminal half-life of 21 hours and the majority of the dose (60–71%) is eliminated unchanged in the urine.

Alogliptin has been investigated in numerous randomised controlled trials in patients whose type 2 diabetes was not adequately managed with diet and exercise or other antidiabetic drugs. Some of these trials are listed in the Table.

Once-daily alogliptin was found to significantly reduce glycated haemoglobin (HbA1c) – a surrogate marker for glycaemic control – when added to stable doses of metformin[1], glibenclamide[2], pioglitazone[3] or insulin (with or without metformin)[4]. HbA1c reductions were also seen when it was added to dual therapy with metformin and pioglitazone[5] (see Table).

As initial therapy, alogliptin was significantly better than placebo at lowering HbA1c.[6] It also showed benefit as initial therapy in combination with pioglitazone[7] (see Table).

During trials, the most common adverse event with alogliptin was pruritus. Headache, diarrhoea, myalgia, rash, musculoskeletal pain, abdominal pain, nausea and infections (influenza, nasopharyngitis, upper respiratory tract infection) were also common (1–10% of patients).

Severe hypersensitivity reactions (e.g. angioedema, Stevens-Johnson syndrome), hepatic failure and pancreatitis have been reported in postmarketing surveillance. Alogliptin is not recommended in patients with severe hepatic impairment.

Hypoglycaemia can occur when alogliptin is added to insulin or a sulfonylurea so these drugs may need to be given at lower doses during combination therapy.

Alogliptin is a category B3 pregnancy drug. There are no data in humans so it is best avoided during pregnancy. Alogliptin was excreted in breast milk in animal studies so there is a risk of exposure to a breastfeeding infant.

Renal function should be assessed before patients start alogliptin. Dose reduction is recommended in patients with moderate (creatinine clearance 30 to 50 mL/min) or severe renal impairment (creatinine clearance <30 mL/min) and those with end-stage renal disease requiring dialysis. Experience in patients with severe renal disease is limited and caution is urged.

As with other DPP4 inhibitors, alogliptin is modestly effective at lowering HbA1c. It provides another option for monotherapy or as an add-on therapy when a patient's diabetes is not controlled by metformin, a sulfonylurea, a thiazolidinedione or insulin. It can also be added as a third option in patients already taking metformin and pioglitazone. Despite showing benefit in trials, alogliptin is currently not indicated for initial combination therapy in Australia.[7]

T T manufacturer provided additional useful information

REFERENCES *†

1. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 008 Group. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract 2009;63:46-55.
2. Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q; Alogliptin Study 007 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. Diabetes Obes Metab 2009;11:167-76.
3. Pratley RE, Reusch JE, Fleck PR, Wilson C, Mekki Q; Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin 2009;25:2361-71.
4. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson C, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA1c without causing weight gain or increased hypoglycaemia. Diabetes Obes Metab 2009;11:1145-52.

* Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

Table **Clinical trials of alogliptin in type 2 diabetes**

Trials	Treatment arms	Mean baseline HbA1c (%)	Mean change in HbA1c (%) from baseline
Add-on studies			
Alogliptin plus metformin[1] for 26 weeks (527 patients)	alogliptin 12.5 mg + metformin	7.9–8.0	-0.60
	alogliptin 25 mg + metformin		-0.60
	placebo + metformin		-0.10
Alogliptin plus a sulfonylurea[2] for 26 weeks (500 patients)	alogliptin 12.5 mg + glibenclamide	8.08	-0.39
	alogliptin 25 mg + glibenclamide	8.09	-0.53
	placebo + glibenclamide	8.15	+0.01
Alogliptin plus a thiazolidinedione[3] (metformin or a sulfonylurea allowed) for 26 weeks (493 patients)	alogliptin 12.5 mg + pioglitazone	8.1	-0.66
	alogliptin 25 mg + pioglitazone	8.0	-0.80
	placebo + pioglitazone	8.0	-0.19
Alogliptin plus insulin[4] (with or without metformin) for 26 weeks (390 patients)	alogliptin 12.5 mg + insulin	9.3	-0.63
	alogliptin 25 mg + insulin		-0.71
	placebo + insulin		-0.13
Alogliptin plus metformin and a thiazolidinedione[5] for 52 weeks (803 patients)	alogliptin 25 mg + metformin + pioglitazone 30 mg	8.3	-0.89 at 26 weeks -0.70 at 52 weeks
	placebo + metformin + pioglitazone 45 mg	8.1	-0.42 at 26 weeks -0.29 at 52 weeks
Initial therapy			
Monotherapy[6] for 26 weeks (329 patients)	alogliptin 12.5 mg	7.9	-0.56
	alogliptin 25 mg		-0.59
	placebo		-0.02
Alogliptin plus a thiazolidinedione[7] for 26 weeks (655 patients)	alogliptin 12.5 mg + pioglitazone 30 mg	8.85	-1.56
	alogliptin 25 mg + pioglitazone 30 mg	8.80	-1.71
	alogliptin 25 mg	8.80	-0.96
	pioglitazone 30 mg	8.76	-1.15

5. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52 week, randomized, double-blind, active-controlled, parallel-group study. Diabetes Obes Metab 2011;13:1088-96.
6. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 010 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycaemic control. Diabetes Care 2008;31:2315-7.
7. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. Diabetes Care 2010;33:2406-8.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).