New drugs

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.

Linagliptin

Approved indication: type 2 diabetes
Trajenta (Boehringer Ingelheim)
5 mg tablets
Australian Medicines Handbook section 10.1.3

Patients with diabetes produce less of the peptide hormones known as incretins. Their concentration can be increased by inhibiting the enzyme (dipeptidyl peptidase 4) which metabolises them. This increases insulin secretion and lowers glucose concentrations. Saxagliptin, sitagliptin, vildagliptin and now linagliptin are all inhibitors of the enzyme (see: Incretin mimetics and enhancers, Aust Prescr 2008;31:102-8).

Linagliptin is taken once a day. Its bioavailability is only 30% and this can be reduced by drugs, such as rifampicin, which induce the P-glycoprotein transporter. The metabolism of the drug involves cytochrome P450 3A4, but this may not be clinically important. Most of the dose is excreted unchanged in the faeces. The terminal half-life of the drug exceeds 100 hours.

Several thousand patients have been involved in trials of linagliptin. These studies included combinations with other treatments for type 2 diabetes as well as monotherapy. In 503 patients with inadequately controlled diabetes, 24 weeks of monotherapy had a significantly greater effect than placebo. From a baseline mean of 8%, the mean glycated haemoglobin (HbA1c) reduced by 0.44% with linagliptin 5 mg, but increased by 0.25% with placebo.[1] In Australia however, linagliptin is only approved in combination with metformin, a sulfonylurea or both.

Another 24-week trial randomised 701 patients whose diabetes was not controlled by metformin. A group of 523 patients took linagliptin and 177 took placebo. From a baseline of 8.09%, the HbA1c reduced by 0.49% with linagliptin 5 mg and increased by 0.15%, from 8.02%, with placebo. A target HbA1c of 7% or less was achieved by 26% of the linagliptin group and 9% of the placebo group.[2]

In a similar group of 333 patients, another placebo-controlled trial studied three different doses (1 mg, 5 mg and 10 mg) of linagliptin and also included a glimepiride arm. All the patients continued to take metformin during the trial. After 12 weeks the active treatments had significantly reduced HbA1c from similar baseline values (see Table).[3] A longer term comparison found that after a year linagliptin 5 mg reduced HbA1c by 0.38% and glimepiride reduced it by 0.6%.

An 18-week trial studied linagliptin in combination with a sulfonylurea. Compared with placebo, the mean treatment difference was 0.47%.

Linagliptin has also been studied, in 1058 patients, as an addition to treatment with metformin and a sulfonylurea. While adding a placebo reduced the mean HbA1c by 0.1% after 24 weeks, linagliptin reduced it by 0.72%.[4]

Adding a drug which increases insulin secretion to the treatment of patients with diabetes increases the risk of hypoglycaemia. In patients taking metformin and a sulfonylurea, hypoglycaemia was reported in 22.7% when linagliptin was added and in 14.8% when a placebo was added.[4]

During monotherapy the adverse events in patients taking linagliptin included musculoskeletal problems, hypertension and headache.[1] Some patients may have increases in triglycerides and uric acid concentrations. Rare adverse events include hypersensitivity reactions and pancreatitis. A meta-analysis of cardiovascular events found no increased risk associated with linagliptin.

Animal studies have shown that linagliptin crosses the placenta and is excreted in breast milk.

Table **Effect of adding linagliptin, glimepiride or placebo to the treatment of patients with type 2 diabetes inadequately controlled by metformin** [3]

	TREATMENT				
	Placebo	Linagliptin 1 mg	Linagliptin 5 mg	Linagliptin 10 mg	Glimepiride 1 mg, 2 mg or 3 mg
Number of patients	71	65	66	66	65
Baseline HbA1c %	8.4	8.2	8.5	8.4	8.2
Change in HbA1c % after 12 weeks	+0.24	−0.14	−0.5	−0.42	−0.68

Linagliptin adds to the choice of drugs which can be considered when a patient's diabetes is not controlled by metformin and sulfonylureas. There seems little difference between the inhibitors of dipeptidyl peptidase, but linagliptin does not require a dose adjustment in patients with renal impairment.

T T manufacturer provided additional useful information

REFERENCES *†A

1. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab 2011;13:258-67.
2. Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2011;13:65-74.
3. Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabet Med 2010;27:1409-19.
4. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. Diabet Med 2011;28:1352-61.

The T-score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* 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).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

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5	False	6	False
7	False	8	False
9	True	10	False
11	False	12	True