

## 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 either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

### Saxagliptin

Onglyza (Bristol-Myers Squibb)

5 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook section 10.1.3

Incretins help to lower blood glucose after a meal. This effect can be prolonged by inhibiting their metabolism. Sitagliptin and saxagliptin are drugs which do this by inhibiting the enzyme dipeptidyl peptidase 4 (DPP4) (see 'Incretin mimetics and enhancers' Aust Prescr 2008;31:102-8).

Saxagliptin is taken once a day. After absorption, the drug suppresses DPP4 activity for 24 hours. Saxagliptin is metabolised by cytochrome P450 3A4 to a less potent active metabolite. The pharmacokinetics of saxagliptin can therefore be affected by other drugs which act on P450 3A4. For example, inhibition by ketoconazole increases the concentration of saxagliptin and decreases the concentration of its active metabolite. Saxagliptin has a half-life of 2.5 hours and its main metabolite has a half-life of 3.1 hours. The drug and its metabolites are mainly excreted in the urine. It should not be used in patients with moderate or severe renal impairment.

Saxagliptin has been studied as an add-on treatment for patients with type 2 diabetes that had not been controlled by a single drug. It was added to metformin in a placebo-controlled study of 743 patients. After 24 weeks of treatment, the 191 patients who took metformin with saxagliptin 5 mg had a reduction of 0.69% in their concentrations of glycated haemoglobin (HbA1c). There was a rise of 0.13% in the patients who added a placebo to metformin. Saxagliptin also significantly reduced fasting blood glucose.<sup>1</sup>

The relative benefits of increasing the dose of a sulfonylurea or adding saxagliptin were assessed in a study of 768 patients. All the patients were given glibenclamide 7.5 mg daily for four weeks. Patients whose diabetes was not controlled were then randomised to increase the dose to 10 mg daily or add saxagliptin 2.5 or 5 mg. After 24 weeks the mean HbA1c concentration had increased by 0.08% in the glibenclamide group, but decreased by 0.54% in patients who added saxagliptin 2.5 mg and by 0.64% in those who added 5 mg. The combination of treatments had a statistically significantly greater effect on fasting blood glucose than increasing the dose of glibenclamide.<sup>2</sup> The mean reduction from baseline was 0.4 mmol/L with saxagliptin 2.5 mg and 0.5 mmol/L with saxagliptin 5 mg,

compared with an increase of 0.04 mmol/L with glibenclamide.

Saxagliptin has also been added to the treatment of patients whose diabetes has not been controlled by a thiazolidinedione. In this study, 565 patients taking pioglitazone or rosiglitazone were randomised to add saxagliptin 2.5 mg, 5 mg or a placebo. After 24 weeks the HbA1c concentration had fallen by 0.66% with 2.5 mg, 0.94% with 5 mg and 0.3% with placebo. The reductions in fasting blood glucose were also significantly greater with saxagliptin.<sup>3</sup>

One study used saxagliptin and metformin in 1306 patients who were starting treatment for the first time. After 24 weeks the combination reduced the concentrations of HbA1c and fasting blood glucose more than either drug alone. Metformin with saxagliptin 5 mg reduced HbA1c by 2.5% compared to 2.0% with metformin and 1.7% with saxagliptin 10 mg alone.<sup>4</sup>

During the trials 3.3% of the patients discontinued saxagliptin 5 mg because of adverse effects compared with 1.8% of the placebo groups. Reasons for stopping treatment included lymphopenia, rashes and increased creatinine concentrations. Hypoglycaemia was reported by 5.2% of patients when saxagliptin 5 mg was added to metformin,<sup>1</sup> 14.6% when added to glibenclamide<sup>2</sup> and 2.7% when added to a thiazolidinedione.<sup>3</sup> In the thiazolidinedione study 8.1% of the patients developed peripheral oedema when saxagliptin 5 mg was added to their treatment.<sup>3</sup>

Saxagliptin's main role is likely to be as an add-on therapy. Its modest efficacy will not bring every patient's diabetes under control. The proportion of patients achieving HbA1c concentrations under 7% after adding saxagliptin 5 mg was 43.5% with metformin,<sup>1</sup> 22.8% with glibenclamide<sup>2</sup> and 41.8% with a thiazolidinedione.<sup>3</sup> Continuing diet and exercise is therefore important. Although saxagliptin has been approved for use with metformin as an initial drug treatment, it is not usual practice to begin treatment with a combination of drugs. As diabetes is a chronic disease, it will be years before the clinical effectiveness and safety of saxagliptin can be confirmed.

**T** manufacturer provided the AusPAR

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## Sertindole

Serdolect (Lundbeck)

4 mg, 12 mg, 16 mg and 20 mg tablets

Approved indication: schizophrenia

Australian Medicines Handbook section 18.2

Sertindole, an atypical antipsychotic drug, was marketed overseas in the 1990s (see 'New antipsychotic medications' *Aust Prescr* 1999;22:81-3). In 1998 the drug was withdrawn from the European market because of concerns that it could cause fatal arrhythmias. It returned to the market several years later after a review of its safety.

Sertindole blocks dopamine D<sub>2</sub>, alpha<sub>1</sub> adrenergic and serotonin 5HT<sub>2</sub> receptors. It has no significant anticholinergic effects and little effect on serum prolactin.

Although sertindole is well absorbed, the absorption is slow. Most of the dose is metabolised and then slowly excreted in the faeces. Severe hepatic impairment is a contraindication. The metabolism involves cytochrome P450 2D6 and 3A so there are potential interactions with drugs such as fluoxetine and erythromycin. Coadministration with inhibitors of P450 3A is contraindicated. The half-life of sertindole varies, because of interindividual variability in metabolism, but averages about three days. While it is suitable for once-daily dosing, there is a delayed onset of action so sertindole is not suitable for emergency treatment of psychosis.

There have been several trials of sertindole and these have been assessed in reviews by the Cochrane Collaboration. The first review included a placebo-controlled study and two comparisons with haloperidol involving a total of 1104 patients with schizophrenia. After 40 days the 54 patients given sertindole 20 mg had improved on a range of rating scales compared to the 48 patients randomised to placebo. The number of patients who needed to be treated for one to be 'very much improved' was approximately eight (confidence interval 4–41, 95% confidence interval). Lower doses were not

significantly better than placebo. One of the comparisons with haloperidol only lasted for a few weeks, but the other continued for one year. After eight weeks the scores on the positive and negative symptoms scale (PANSS) were similar for both drugs. Although the mean improvement in the PANSS scores after a year was greater for sertindole, this difference was not statistically significant.<sup>1</sup>

The second review attempted to compare sertindole with other atypical antipsychotics but only included two low quality comparisons with risperidone. These studies involved 508 patients, but only lasted for 12 weeks. There was no clear difference in efficacy.<sup>2</sup>

The extrapyramidal adverse effects of sertindole were similar to those of placebo and less than with haloperidol.<sup>1</sup> Sertindole caused less akathisia and parkinsonism than risperidone, but some of the patients had been given high doses of risperidone.<sup>2</sup>

Both reviews reported on prolongation of the QTc interval on the ECG. More patients taking sertindole had QTc prolongation than those taking placebo, haloperidol or risperidone.<sup>1,2</sup> All patients should have an ECG at baseline before treatment as a prolonged QTc interval is a contraindication. ECG monitoring is mandatory during treatment, particularly around the time of changes in dose. Prolongation of the QTc interval is an indication to reduce or stop treatment. Many drugs can prolong the QTc interval, and they should not be used by patients taking sertindole. In addition to regular monitoring of the ECG, patients need to be checked for hypokalaemia and hypomagnesaemia. These electrolyte disturbances are contraindications to treatment with sertindole.

As sertindole blocks alpha<sub>1</sub> adrenergic receptors it can cause postural hypotension. Treatment should therefore begin at a low dose and be increased slowly.

Patients taking sertindole are likely to put on weight. In trials where patients took 24 mg daily for 12 months, 21% gained at least 15% of their baseline weight.

Other adverse effects which occur significantly more often with sertindole than placebo include dizziness, paraesthesia, peripheral oedema and abnormal ejaculation. The safety of sertindole in pregnancy and lactation is uncertain.

Considering the concerns about safety, 8600 patients who had been treated with sertindole were followed up in a company-sponsored study. There were 3819 person-years of exposure with 35 deaths including 11 from cardiac causes and eight suicides.<sup>3</sup> The all-cause mortality rate was 0.92 per 100 person-years of exposure. Cardiovascular and metabolic diseases (including diabetes) were associated with a higher risk of premature cardiac or unexplained death. Sertindole is therefore contraindicated in patients with cardiovascular disease.

An open-label prospective study followed approximately 10 000 patients treated with sertindole or risperidone. Although there

was no significant difference in suicide, cardiac mortality was higher with sertindole. There were 31 deaths from cardiac causes in the sertindole group and 12 in the risperidone group.<sup>4</sup> Although sertindole has been back on the European market for several years there are many limitations to its use. In view of the safety concerns sertindole should only be used by patients who cannot tolerate or do not respond to other antipsychotic drugs.

**T** manufacturer provided the product information

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The T-score (**T**) is explained in 'New drugs: T-score for transparency' in this issue, *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](http://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](http://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](http://www.tga.gov.au/industry/pm-auspar.htm))

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## Answers to self-test questions

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|---------|----------|---------|
| 1. True | 3. False | 5. True |
| 2. True | 4. False | 6. True |

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