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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

5. The effectiveness of bisphosphonates in preventing hip fracture in patients taking corticosteroids is unknown.
6. Calcium prevents the rapid loss of bone mineral density in patients starting corticosteroids.

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.

Lenalidomide

Revlimid (Celgene)

5 mg, 10 mg, 15 mg and 25 mg capsules

Approved indication: multiple myeloma

Australian Medicines Handbook section 14.3

Multiple myeloma is a cancer of plasma cells in bone marrow. This disease is characterised by increased levels of paraprotein, an abnormal type of immunoglobulin produced by tumour cells. Multiple myeloma is incurable with conventional treatments and the median survival time after diagnosis is 3–5 years.¹ Modern treatments such as bone marrow transplant, bortezomib (*Aust Prescr* 2006;29:84-7) and thalidomide (*Aust Prescr* 2003;26:146-51) have improved the prognosis.

Lenalidomide is an analogue of thalidomide. Its mechanism of action is not clearly understood although it is thought to modulate the immune system. It inhibits proliferation of certain haematopoietic tumour cells, prevents the growth of blood vessels within tumours and induces proliferation of specialised immune cells that attack cancerous cells.

Following oral administration in patients with multiple myeloma, lenalidomide is rapidly absorbed and maximum plasma concentrations are reached within 0.5–4 hours. In healthy volunteers, its elimination half-life increases with dose from about three hours with 5 mg up to nine hours with 400 mg. Most of the drug is excreted unchanged in urine. Lenalidomide should be taken at least one hour before or two hours after food.

In studies of multiple myeloma, patient responses are generally judged by changes in concentrations of paraprotein. In an open-label trial, the efficacy of lenalidomide was investigated in patients with relapsed or relapsed and refractory multiple myeloma. Responses were observed in 1 of 5 patients given

10 mg/day lenalidomide, 2 of 3 patients given 25 mg/day and 12 of 13 patients given 50 mg/day.²

In another trial, patients with relapsed or relapsed and refractory multiple myeloma received either 30 mg lenalidomide once daily (67 patients) or 15 mg lenalidomide twice daily (35 patients) for 21 days of a 28-day cycle. Patients with stable or progressive disease after two cycles of treatment had dexamethasone added. Overall, 25% of patients responded to lenalidomide treatment. Four patients had a complete response in the once-daily group, whereas there were no complete responses in the twice-daily group. During the trial, 68 of the 102 patients had dexamethasone added and 20 of these patients responded to the addition. The median progression-free survival time was 7.7 months with the single dose of lenalidomide and 3.9 months with the twice-daily dose.³

In two phase III trials totalling 704 patients with relapsed or refractory multiple myeloma, lenalidomide (25 mg once daily for 21 days of a 28-day cycle) or placebo was added to dexamethasone treatment (40 mg). Results were similar in each trial with more patients taking lenalidomide plus dexamethasone responding to treatment compared to those taking dexamethasone alone (approximately 61% vs 22%). Median time to progression was around 11 months with combination therapy compared to just under 5 months with dexamethasone alone.^{4,5}

Monitoring of complete blood counts is recommended because neutropenia and thrombocytopenia are very common with lenalidomide (especially when used with dexamethasone) and patients often need their dose to be reduced or interrupted. Growth factors may be needed for patients with neutropenia. There is also an increased risk of deep vein thrombosis and pulmonary embolism in patients taking lenalidomide with

dexamethasone so patients and doctors should be vigilant for symptoms. Erythropoietic drugs or drugs that increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution. Prophylactic measures may be needed in high-risk patients.

Other adverse events associated with lenalidomide (30 mg once daily) include constipation (25% of patients), anaemia (16%), peripheral neuropathy (10%), fatigue (7%) and diarrhoea.³ Lenalidomide is renally excreted, so the risk of adverse events is expected to be greater in patients with impaired renal function.

Lenalidomide increases the plasma exposure of digoxin, so it is advisable to monitor digoxin concentrations if these drugs are taken concomitantly. As fatigue, dizziness, somnolence and blurred vision have been reported with lenalidomide, caution is recommended when driving or operating machinery.

Due to its structural similarity with thalidomide, lenalidomide is a potential teratogen and should be avoided during pregnancy. Male patients should use condoms throughout treatment and for one week after cessation. Lenalidomide is only available under a restricted distribution program. Doctors and pharmacists must be registered in the program before they can prescribe or dispense the drug.

Lenalidomide is indicated for the treatment of multiple myeloma in patients who have received at least one prior therapy, and who have progressive disease. Its effectiveness seems to be higher when used in combination with dexamethasone and investigations are under way for its use in combination with other treatments such as doxorubicin and vincristine. Using lenalidomide with dexamethasone for newly diagnosed multiple myeloma is also being studied.¹

 manufacturer declined to supply data

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Nilotinib

Tasigna (Novartis)

200 mg capsules

Approved indication: chronic myeloid leukaemia

Australian Medicines Handbook section 14.2.2

Most patients who develop chronic myeloid leukaemia have an abnormal chromosome called the Philadelphia chromosome (Ph) (Aust Prescr 2006;29:76-9). This is caused by a genetic translocation of chromosomes 9 and 22. The presence of this mutation leads to the production of an abnormal tyrosine kinase which causes cells to become malignant.

The majority of patients with newly diagnosed chronic myeloid leukaemia benefit from treatment with the tyrosine kinase inhibitor imatinib. However, resistance to imatinib can arise, for example from point mutations in the tyrosine kinase which cause interference with imatinib binding.

Nilotinib is a new tyrosine kinase inhibitor which has been rationally designed to have a more selective action than imatinib. It prevents proliferation of malignant cells by binding to the abnormal tyrosine kinase. In *in vitro* studies, nilotinib has been shown to inhibit the growth of 32 out of 33 imatinib-resistant cell lines. However, it is not effective against cell lines carrying the T3151 mutation.

After oral administration, peak concentrations of nilotinib are reached within three hours. Nilotinib should be taken on an empty stomach and food should not be eaten for at least two hours before and one hour after the dose. This is because the bioavailability of nilotinib is increased with food therefore the risk of toxicity is increased. The drug is metabolised mainly by cytochrome P450 3A4 and is excreted in the faeces unchanged and as metabolites.

Cytochrome P450 3A4 inhibitors (such as ketoconazole, erythromycin and grapefruit products) and inducers (such as corticosteroids, rifampicin and St John's wort) may alter serum levels of nilotinib and should be avoided. Nilotinib increases the risk of toxicity from other cytochrome P450 3A4 substrates such as simvastatin. Caution should be used with warfarin. Drugs that prolong the QT interval, such as clarithromycin and haloperidol, should be avoided with nilotinib.

An initial dose-escalation trial of nilotinib showed benefits in patients with chronic myeloid leukaemia who were resistant to imatinib therapy. Nilotinib was found to be less effective in patients with blastic-phase chronic myeloid leukaemia than those in the chronic or accelerated phase of the disease.¹

Two open-label phase II trials of nilotinib (400 mg twice daily) have been conducted in patients with either chronic-phase² or accelerated-phase³ chronic myeloid leukaemia who had failed to respond or were intolerant to imatinib therapy.

In the chronic-phase disease trial, around half of the patients (134 of 280) had a major cytogenetic response (0-35% Ph-positive cells in the bone marrow) to nilotinib. The median time

for this response was 2.8 months. A complete haematologic response (measured by counting white blood cells, platelets, blasts, myelocytes and metamyelocytes in peripheral blood) was achieved by 74% of evaluable patients.²

In the trial of accelerated-phase disease, about a third of patients (35 of 119) had a major cytogenetic response to nilotinib and 26% (31 of 119) had a complete haematologic response after a median of seven months treatment.³ (In this trial, a third of the 119 patients had not been assessed for a haematologic response at the time of data collection.)

Nilotinib appeared to overcome imatinib resistance in many patients in these trials. However, as predicted from *in vitro* studies, almost all of the patients (7 of 8) carrying the T3151 mutation were resistant to nilotinib treatment.^{1,2,3}

During the clinical trials, neutropenia and thrombocytopenia were seen in up to a third of patients. These were usually managed by reducing or interrupting the nilotinib dose with some patients requiring haematopoietic growth factors or platelet transfusions. As myelosuppression is common with nilotinib, complete blood counts should be performed every two weeks for the first two months and then monthly after that.

Rash, pruritus, nausea, constipation, fatigue and headache were commonly reported.^{1,2,3} Elevations in bilirubin, aspartate aminotransferase and alanine aminotransferase have been observed at daily doses of 600 mg or more. Increased concentrations of serum lipase and amylase have also been reported and caution is recommended in patients with a history of pancreatitis.

Nilotinib can potentially prolong the QT interval and sudden deaths with this drug have occurred, therefore it should not be used in patients with prolonged QT interval. Electrolyte abnormalities, such as hypokalaemia and hypomagnesaemia, should be corrected before a patient starts nilotinib.

For patients who are resistant to imatinib or cannot tolerate it, nilotinib offers a second-line treatment option along with another recently approved drug, dasatinib (see New drugs, Aust Prescr 2007;30:50–5). However, like dasatinib, nilotinib is not effective for patients carrying the T3151 mutation. It is not known how nilotinib directly compares with dasatinib, but a trial of 23 patients showed that dasatinib may be effective when nilotinib therapy has failed.⁴

T manufacturer provided only the product information

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Paliperidone

Invega (Janssen-Cilag)

3 mg, 6 mg and 9 mg modified-release tablets

Approved indication: schizophrenia

Australian Medicines Handbook section 18.2.2

Risperidone is an antipsychotic drug which is at the end of its patent. Its manufacturer is now marketing one of its metabolites, paliperidone.

When risperidone is metabolised by cytochrome P450 2D6 it produces 9-hydroxy-risperidone (paliperidone) which exists as two enantiomers. The activity of paliperidone is similar to that of risperidone because it binds to dopamine (D₂) and serotonin (5HT_{2A}) receptors.

The tablets of paliperidone are designed to slowly release the drug into the gut. They should not be crushed or broken to assist swallowing. Although food increases bioavailability, the once-daily dose does not have to be taken with meals. However, patients are advised not to alternate taking the drug with or without food. It takes 24 hours to reach the peak plasma concentration and the elimination half-life is of a similar duration. Most of the drug is excreted unchanged in the urine. Lower doses are needed if renal function is reduced.

In a six-week trial, 628 patients with acute schizophrenia were randomised to take a placebo, 10 mg olanzapine or one of three doses of paliperidone (6 mg, 9 mg, 12 mg). The atypical antipsychotics had a significantly larger effect than placebo on the patients' scores on the Positive and Negative Syndrome Scale (PANSS). The mean baseline score of 94 was reduced by 4.1 with placebo, 19.9 with olanzapine, and by 17.9, 17.2 and 23.3 with 6 mg, 9 mg and 12 mg paliperidone respectively.¹ Two other six-week studies produced similar results. As it is unclear that higher doses are significantly more effective, the recommended dose of paliperidone is 6 mg taken each morning.

A double-blind, randomised trial looked at paliperidone in the prevention of symptom recurrence. After 207 patients with schizophrenia were stabilised on paliperidone they either continued treatment or were switched to a placebo. The trial was stopped prematurely because a significant difference in efficacy emerged. At the time of the halt the median duration of treatment was 29 days with placebo and 45 days with paliperidone. Schizophrenia symptoms had recurred in 53% of

the placebo group and 25% of the paliperidone group.²

The adverse effects of paliperidone are similar to those of risperidone. Extrapyramidal symptoms common to both drugs include tremor, akathisia and dystonia. Other frequent adverse events include headache, somnolence, tachycardia and orthostatic hypotension. The six-week study was too short to show significant changes in metabolism, but a weight increase of 7% or more was seen in 5% of the patients taking paliperidone 6 mg compared with 2% of the placebo group.¹ In the recurrence study 20% of the paliperidone group and 12% of the placebo group added at least 7% of their body weight.² This will add to the risk of developing diabetes.³ An increase in serum prolactin with paliperidone may have the same effect as risperidone, which is associated with an increased risk of tumours in animal studies. As paliperidone can cause a small increase in the QT interval it is not recommended for use with drugs which have a similar effect on the ECG.

While paliperidone is better than placebo in short-term studies, schizophrenia is a long-term illness. Much more is known about risperidone. As paliperidone is a product of the cytochrome P450 system it is not expected to cause interactions with other drugs metabolised by this system. While dose titration is not required at the start of therapy, any advantage of paliperidone over risperidone would be unlikely to justify a higher price. Paliperidone is not approved for patients with dementia-related psychosis.

T T manufacturer provided additional useful information

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Raltegravir

Isentress (Merck Sharp & Dohme)

400 mg tablets

Approved indication: HIV infection

Australian Medicines Handbook section 5.4

The main classes of antiretroviral drugs inhibit viral enzymes such as reverse transcriptase and protease. Combinations of reverse transcriptase inhibitors and protease inhibitors are effective, but this treatment eventually fails. Drugs acting on other parts of the HIV life cycle are therefore needed to regain control of the patient's viraemia.

The replication of HIV requires viral DNA to be inserted into the genome of the host cells. This process involves HIV integrase, so inhibiting this enzyme should impede viral replication. Raltegravir is the first integrase inhibitor to be approved in Australia.

In a dose-ranging study, 35 patients took raltegravir or a placebo for 10 days. The concentration of viral RNA declined significantly more with the drug than with placebo, paving the way for phase II trials.¹

One trial randomised 179 patients to take a placebo or one of three doses of raltegravir twice daily. These patients had been treated for a median of 10 years, but their viral RNA load was greater than 5000 copies/mL. They took an 'optimised background regimen' of 2-7 antiretroviral drugs in addition to their randomised therapy. After 24 weeks 13% of the placebo group had less than 50 copies/mL. This response was achieved by significantly more of the patients taking raltegravir; 65% with 200 mg, 56% with 400 mg and 67% with 600 mg. There was also a significant increase in CD4 cell counts. With the recommended dose of 400 mg twice daily, there was a mean increase of 113 cells/microlitre compared with an increase of 5 cells/microlitre with placebo.²

The approval of raltegravir is based mainly on the interim results of two phase III trials. These trials had the same design and enrolled previously treated patients infected with HIV resistant to three different classes of antiretroviral drugs. In total, 462 patients added raltegravir to their optimised background regimen and 237 added a placebo. After 16 weeks 436 patients had been treated or discontinued. HIV RNA had fallen below 50 copies/mL in 61-62% of the patients taking raltegravir compared with 33-36% of the placebo group. CD4 cell counts increased by 83-86 cells/mm³ with raltegravir and by 31-40 cells/mm³ with placebo. These differences remained at the 24-week analysis.

Adverse events in patients taking multiple drugs are common. Adding raltegravir did not appear to cause more adverse effects than adding a placebo. Only 2% of patients discontinued treatment because of adverse events. Serious adverse events occurring in the trials included hypersensitivity reactions, hepatitis, anaemia, myocardial infarction and renal failure.

The pharmacokinetics of raltegravir are variable and its bioavailability is unknown. Raltegravir is probably cleared by glucuronidation with most of the dose being eliminated in the faeces. The terminal half-life is approximately nine hours. Atazanavir inhibits glucuronidation so it will increase concentrations of raltegravir, however no dose adjustment has been recommended for patients taking raltegravir with a combination of atazanavir and ritonavir. The combination of tipranavir and ritonavir reduces concentrations of raltegravir, but no dose adjustment is recommended.

Although the final results of the phase III trials are currently unpublished, raltegravir has a significant effect on the markers

of HIV infection. Whether this improves the patient's prognosis remains to be seen. Longer-term follow-up is also needed to assess the development of viral resistance and long-term adverse events such as cancer. Although raltegravir has been studied in previously untreated patients³, this indication is not approved.

X manufacturer did not respond to request for data

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Rotigotine

Neupro (UCB Pharma)

transdermal patches releasing 2 mg, 4 mg, 6 mg or 8 mg per 24 hours

Approved indication: Parkinson's disease

Australian Medicines Handbook section 16.2

Parkinson's disease is characterised by a progressive loss of dopaminergic neurons in the brain, causing patients to develop tremor, rigidity and bradykinesia. Symptomatic treatment using drugs such as levodopa and dopamine agonists (*Aust Prescr* 2001;24:92-5) aims to restore dopaminergic stimulation of the striatal neurons.

Rotigotine is a new non-ergot dopamine agonist which acts at dopamine receptors D₃, D₂ and D₁. In Australia, it has been approved as a monotherapy or in combination with levodopa for early to advanced Parkinson's disease.

This drug comes in the form of a skin patch which is applied once a day. About 45% of the rotigotine in the patch is released within 24 hours and steady state plasma concentrations are reached by 1-2 days. After being extensively metabolised, rotigotine is mainly excreted in the urine as metabolites. Once the patch is removed, plasma concentrations decrease with a terminal half-life of 5-7 hours.

In an eleven week dose-finding trial of 242 patients with early Parkinson's disease, there was a significant improvement in activities of daily living and motor function of patients who received rotigotine 6 mg/24 hours or 8 mg/24 hours compared

to placebo.¹ In a six-month study of 272 similar patients, the proportion of participants who had a 20% improvement was higher with rotigotine (2 mg, 4 mg or 6 mg/24 hours) than with placebo (48% vs 19%).²

Rotigotine has been compared with ropinirole in 561 patients with early Parkinson's disease. Ropinirole is also a dopamine agonist, but is not currently approved for Parkinson's disease in Australia. Although rotigotine was better than placebo (with 52% vs 30% of patients responding), it did not appear to be as effective as ropinirole (to which 68% of patients responded).³

Rotigotine has also been tested in patients with advanced Parkinson's disease who were already taking levodopa (≥ 200 mg/day) and had poorly controlled symptoms with at least 2.5 hours of 'off' time a day.^{4,5} After 24 weeks of maintenance treatment, there were more responders (patients with 30% or more reduction in 'off' time) with rotigotine (8 mg/24 hours or 12 mg/24 hours) than with placebo (56% vs 35%).⁴ In another trial, rotigotine (up to 16 mg/24 hours) appeared to be as effective as pramipexole (up to 4.5 mg/day orally) after 16 weeks of maintenance treatment. Responder rates were 60% for rotigotine (120 of 201 patients), 67% for pramipexole (134 of 200 patients) and 35% for placebo (35 of 100 patients).⁵

Rotigotine's safety profile is generally typical of a dopamine agonist. In a trial of early Parkinson's disease, the most commonly reported adverse events with doses of 2-8 mg/24 hours were nausea (47% of patients), application-site reactions (39%), dizziness (24%), somnolence (22%), insomnia (19%), headache (17%), vomiting (16%) and fatigue (15%). Nausea, application-site reactions, somnolence and insomnia appeared to be dose-related.¹ Approximately 13% of 649 patients receiving rotigotine discontinued treatment because of adverse events. The most common reasons were application site reaction (5%), nausea (2%) and vomiting (1%). When tested as an adjuvant to levodopa in patients with advanced Parkinson's disease, rotigotine was associated with an increase in hallucinations and dyskinesia compared to placebo.^{4,5}

Patients should be warned about the potential sedating effects of rotigotine, which include somnolence and falling asleep suddenly. Some patients have reported sudden sleep or loss of consciousness while driving. Compulsive behaviours such as pathological gambling and increased sexual urges have occurred in patients taking rotigotine.

Rotigotine can elevate heart rate and blood pressure and cause orthostatic hypotension. Monitoring of blood pressure is advisable, especially at the beginning of treatment. Peripheral oedema has been reported in some patients on rotigotine. Patients should be monitored for skin cancers because of an increased risk of melanoma. Cardiac valvulopathy and retinal degeneration may also be a risk with rotigotine.

Dopamine antagonists such as antipsychotics or metoclopramide could potentially reduce the effectiveness of rotigotine and should be avoided.

Rotigotine should be started at 2 mg/24 hours for early Parkinson's disease and 4 mg/24 hours for advanced disease. The dose should be increased weekly depending on the clinical response and tolerability. Likewise, when stopping treatment the dose of rotigotine should be decreased gradually to avoid precipitating neuroleptic malignant syndrome. After removal, the patch is to be folded over so that it sticks to itself before being disposed of safely, and patients or carers should wash their hands to remove any drug.

Rotigotine offers another treatment option for patients with Parkinson's disease. A once-a-day skin patch may be preferable to taking tablets for some patients.

T manufacturer provided only the product information

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Sitagliptin

Januvia (Merck Sharp & Dohme)

25 mg, 50 mg and 100 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook section 10.1.3

Incretins stimulate the release of insulin after meals. They are rapidly metabolised by dipeptidyl peptidase 4 (DPP4) so inhibiting this enzyme prolongs their effect (see Experimental and clinical pharmacology, *Aust Prescr* 2008. In press).

Sitagliptin is an inhibitor of DPP4 which can be given once a day. The drug is rapidly absorbed and its action leads to lower blood glucose concentrations. Its half-life is approximately 12 hours and most of the dose is excreted unchanged in the urine. While people with liver disease may be able to take sitagliptin, it is not recommended for patients with renal impairment.

Several doses of sitagliptin were compared to placebo and glipizide in 743 patients with type 2 diabetes. The patients' mean glycated haemoglobin (HbA1c) at the start of the study was 7.9%. After 12 weeks a total daily dose of sitagliptin 100 mg

had reduced the HbA1c by 0.54%, while there had been a 0.23% increase with placebo. Glipizide reduced HbA1c by 0.76%.¹

Another placebo-controlled study gave sitagliptin to 741 patients for 24 weeks. The mean HbA1c was reduced from 8.0% to 7.39% in the patients who took sitagliptin 100 mg. It fell below 7% in 41% of those taking this dose, compared with 17% of the placebo group.²

A trial involving patients whose type 2 diabetes was inadequately controlled by metformin randomised 464 to add sitagliptin and 237 to add a placebo. The HbA1c declined in the first 12 weeks of sitagliptin therapy then plateaued. After 24 weeks the mean HbA1c had declined from 7.96% to 7.26% with sitagliptin while it was almost unchanged in the placebo group. The HbA1c fell below 7% in 47% of the sitagliptin group, but in only 18% of the placebo group.³

Another study tried starting the treatment of 1091 patients with sitagliptin, metformin or a combination of both. The drugs were given in a variety of doses all of which significantly reduced the mean HbA1c (8.8%) over 24 weeks. The reductions were 0.66% with sitagliptin 100 mg, 0.82% with metformin 500 mg twice daily and 1.13% with metformin 1 g twice daily. In combination therapy, sitagliptin 50 mg twice daily reduced HbA1c by 1.4% with metformin 500 mg twice daily and by 1.9% with metformin 1 g twice daily.⁴

Patients whose diabetes was not controlled by metformin were enrolled in a trial comparing sitagliptin with a sulfonylurea. Glipizide was added to the treatment of 584 patients while 588 added sitagliptin. After a year the average HbA1c declined by 0.56% with glipizide, and 0.51% with sitagliptin. There was a difference in the effect of treatment on the patients' weights. People taking glipizide gained 1.1 kg while those taking sitagliptin lost 1.5 kg.⁵

Sitagliptin has also been added to the treatment of 353 patients taking pioglitazone. At the start of the placebo-controlled trial these patients had mean HbA1c concentrations of approximately 8%. In the 175 randomised to add sitagliptin 100 mg daily for 24 weeks the HbA1c fell by 0.85%. The fall in the placebo group was 0.15%. By the end of the trial 45% of the patients taking sitagliptin and pioglitazone had HbA1c concentrations below 7% compared with 23% of the patients taking pioglitazone and a placebo.⁶

During the trials of sitagliptin the main adverse events were gastrointestinal upsets and musculoskeletal complaints. There were slightly more infections in the patients given sitagliptin. This could be a concern as DPP4 is found in T-lymphocytes. Serious hypersensitivity reactions have also been reported. Hypoglycaemia can occur, but is more likely to happen if sitagliptin is used in combination with a sulfonylurea. Approximately 12% of patients reported hypoglycaemia when sitagliptin was used in combination with glimepiride, with or without metformin.

Sitagliptin has little effect on lipids and its influence on cardiovascular disease in diabetes is unknown. It has an effect

on the surrogate outcome of HbA1c, but its role in therapy is currently unclear. In the comparison with glipizide more patients taking sitagliptin discontinued treatment, mainly because of a lack of efficacy.⁵ Although sitagliptin has a greater effect than placebo, it has not been approved for monotherapy in Australia. It is also not approved as an add-on therapy when a patient's diabetes has not been controlled by the standard therapy of metformin and a sulfonylurea.

manufacturer did not respond to request for data

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The T-score () is explained in 'New drugs: transparency', *Aust Prescr* 2007;30:26-7.

* 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.emea.europa.eu).

Answers to self-test questions

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

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