

7. Clinical exercise testing. In: Franklin BA, editor. Guidelines for exercise testing and prescription. American College of Sports Medicine. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2000.
8. General principles of exercise prescription. In: Franklin BA, editor. Guidelines for exercise testing and prescription. American College of Sports Medicine. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2000.
9. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377-81.

### Further reading

Bowen K. Managing foot infections in patients with diabetes. *Aust Prescr* 2007;30:21-4.

*Conflict of interest: none declared*

### Self-test questions

*The following statements are either true or false (answers on page 135)*

7. High intensity exercise may cause haemorrhage in patients with diabetic retinopathy.
8. Patients with diabetes who have cardiovascular disease are precluded from undertaking an exercise program.

## New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been 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.

### Human papillomavirus vaccine

Cervarix (GlaxoSmithKline)

vial or syringe containing 0.5 mL liquid

Approved indication: prevention of human papillomavirus infection and associated genital disease

Australian Medicines Handbook section 20.1

This is the second vaccine to be registered in Australia against human papillomavirus infection. Like the first vaccine (see New drugs, *Aust Prescr* 2006;29:138-43), this product is not a live vaccine but is made up of virus-like particles derived from the major capsid (L1) protein. It is a bivalent vaccine, designed to protect against human papillomavirus types 16 and 18. These virus types are responsible for around 70% of invasive cervical cancers worldwide and are the most common oncogenic papillomavirus types isolated from Australian women.

The bivalent vaccine has been compared to placebo in a randomised trial of 1113 North American and Brazilian women aged 15-25 years. These women were negative for type 16 or 18 DNA (by the polymerase chain reaction) and seronegative for virus types 16 and 18 at screening. Three doses of the vaccine or placebo were given, at 0, 1 and 6 months. Cervical and cervicovaginal specimens (taken at 3 or 6 month intervals) were analysed for human papillomavirus DNA and abnormal cytology for up to 27 months after the first injection.<sup>1</sup>

After 27 months, there were four cases of persistent infection with type 16 or 18 human papillomavirus in the vaccinated group (560 women) compared to 31 cases in the placebo group (553 women). Two women in the vaccine group had cytological abnormalities associated with virus type 16 or 18 compared to 27 women in the placebo group.<sup>1</sup> These abnormalities included

atypical squamous cells of undetermined significance and low- and high-grade squamous intraepithelial lesions.

A follow-up study continued to monitor the women. Some of them were followed in total for approximately 48 months. These women had received all three doses of the vaccine or placebo and their treatment allocation was still double blind. In the follow-up phase, 10 out of 340 women had persistent human papillomavirus type 16 or 18 infection (for 10 months or longer) in the placebo group compared with none of the 357 women in the vaccine group.<sup>2</sup>

During the combined initial and follow-up phases of the trial, there were four cases of abnormal cytology or histology associated with type 16 or 18 virus in the vaccine group and 83 cases in the placebo group. There were no cases of cervical intraepithelial neoplasia in the vaccine group.<sup>2</sup>

There seemed to be some cross-protection of the vaccine against infection with other human papillomavirus types, particularly types 45 and 31. This corresponded to fewer cases of cytological and histological abnormalities in the vaccine group compared to the placebo group.<sup>2</sup>

There were no vaccine-related serious adverse events reported. However, there were more injection-site symptoms (pain, swelling, redness) in the vaccine group compared to the placebo group.<sup>1,2</sup>

The vaccine should be given intramuscularly in the deltoid region at 0, 1 and 6 months. The second dose can be delayed for up to 2.5 months after the first dose if necessary. The need for booster doses is currently unknown.

This bivalent vaccine appears to be effective in providing long-term protection against human papillomavirus types 16

and 18 infections and the precancerous lesions associated with them. The previously approved vaccine is quadrivalent and contains antigens from virus types 6, 11, 16 and 18. As human papillomavirus types 6 and 11 cause genital warts, the quadrivalent vaccine is indicated for males and females whereas the bivalent vaccine is only indicated for females, but for a wider age range (10–45 years).

**T** manufacturer provided only the product information

## References

1. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;364:1757-65.
2. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006;367:1247-55.

## Insulin glulisine

Apidra SoloStar (sanofi-aventis)

100 IU/mL in 3 mL cartridges for use in reusable insulin injection device

Approved indication: diabetes mellitus

Australian Medicines Handbook section 10.1.1

Insulin analogues are genetically engineered to try and improve the control of blood glucose in patients with diabetes.<sup>1</sup> Insulin glulisine differs from human insulin by only two amino acids. This difference results in a more rapid and short-acting effect on blood glucose.

Patients can inject insulin glulisine in the 15 minutes before, or immediately after, a meal. The analogue reaches a higher maximum concentration faster than a subcutaneous injection of regular human insulin (55 vs 82 minutes) in type 1 diabetes. In type 2 diabetes, the median time to maximum concentration is 89 minutes with insulin glulisine and 94 minutes with insulin. Insulin glulisine is also eliminated more rapidly with a half-life of 42 minutes compared with 86 minutes for regular insulin. Although the maximum concentration of insulin glulisine is approximately twice that of regular insulin, one unit of insulin glulisine has the same glucose-lowering effect as one unit of regular insulin.

Insulin glulisine needs to be used with a longer-acting insulin to provide the patient's basal requirements. It should not be mixed with other insulins (except NPH insulins) before injection.

A comparative study, in patients with type 1 diabetes using insulin glargine for their basal requirements, found that the efficacy of insulin glulisine was similar to that of insulin lispro (another quickly absorbed analogue). In patients with type 2 diabetes using NPH insulin, injecting insulin glulisine 15 minutes or less before meals had a similar effect on glycaemic control to injecting regular insulin 30–45 minutes before meals.

Insulin glulisine has the same adverse reactions as other insulin preparations, but long-term experience is more limited. It has not been approved for use in children less than 12 years, but the reasons are not clear.

**T** manufacturer provided only the product information

## Reference \* †

1. Phillips P. Insulins in 2002. *Aust Prescr* 2002;25:29-31.

## Lapatinib

Tykerb (GlaxoSmithKline)

250 mg tablets

Approved indication: breast cancer

Australian Medicines Handbook section 14.3.9

Lapatinib is a new drug for use in combination chemotherapy with capecitabine for patients with metastatic breast cancer. It is indicated for patients with tumours overexpressing HER2 (human epidermal growth factor receptor type 2) that have progressed after treatment with an anthracycline, a taxane and trastuzumab. Lapatinib causes growth arrest or cell death of tumour cells by reversibly inhibiting the intracellular tyrosine kinase domain of HER1 (human epidermal growth factor receptor type 1) and HER2.

Following oral administration of lapatinib, peak plasma concentrations are reached after approximately four hours. It is extensively metabolised, primarily by CYP3A4 and CYP3A5, then eliminated in the faeces.

Concomitant use of drugs that inhibit or induce CYP3A4, such as ketoconazole or carbamazepine, affects lapatinib's pharmacokinetics so dose adjustment of lapatinib with these drugs may be needed. The systemic exposure of lapatinib is increased in patients with moderate to severe hepatic impairment. As the bioavailability of lapatinib is increased with food, it should be taken at least one hour before or after eating.

Preliminary studies have indicated that lapatinib has biological and clinical activity against various solid tumours (including breast, ovarian and lung) that overexpress HER1 and HER2.<sup>1,2</sup> An interim analysis of the efficacy and safety of lapatinib in combination with capecitabine has been further evaluated in an open label phase III trial. In the study, 324 women with progressive HER2 positive locally advanced or metastatic breast cancer who had already tried other treatments (including an anthracycline, a taxane and trastuzumab) were randomised (in a 1:1 ratio) to receive either a lapatinib plus capecitabine combination or capecitabine alone. Lapatinib was given as a 1250 mg continuous daily dose and capecitabine was given as 2000 mg (when in combination) or 2500 mg (as monotherapy) per square metre of body surface in two divided doses for 14 days of a 21-day cycle.<sup>3</sup>

Clinical data were collected for 20 months after the enrolment of the first patient. During this period, data from 274 of the 324 enrolled women were collected for evaluation.

Overall survival rates were similar in both groups, with 36 deaths in the lapatinib plus capecitabine group and 35 in the capecitabine group. The overall response rate was 22% in the combination group and 14% in the monotherapy group. Patients on combination therapy had a longer median time to disease progression or death compared to those taking capecitabine alone (8.4 months vs 4.4 months).<sup>3</sup>

Diarrhoea was more common in women taking lapatinib plus capecitabine compared to those taking capecitabine alone (60% vs 39%). Dyspepsia and rash were also more common in the combination treatment group. Hand-foot syndrome, nausea and vomiting occurred to a similar degree in both groups. There were five fatal adverse events in the study – two women on combination treatment and three women on monotherapy. The death of a patient with diarrhoea, vomiting and small-bowel obstruction in the monotherapy group was deemed to be related to the study drug.<sup>3</sup>

Lapatinib has been associated with decreases in left ventricular ejection fraction, and asymptomatic cardiac events were detected in 2% of patients taking combination therapy in the trial.<sup>3</sup> Patients should therefore be evaluated before starting therapy and at 8–12 week intervals during treatment to ensure that cardiac function does not decline.

Although lapatinib in combination with capecitabine prolongs the time to disease progression in women with metastatic breast cancer, it does not actually improve overall survival rates compared to capecitabine on its own.

**T** manufacturer provided only the product information

## References \*

1. Spector NL, Xia W, Burris H, Hurwitz H, Dees EC, Dowlati A, et al. Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. *J Clin Oncol* 2005;23:2502-12.
2. Burris HA, Hurwitz HI, Dees EC, Dowlati A, Blackwell KL, O'Neil B, et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol* 2005;23:5305-13.
3. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733-43.

The T-score (**T**) is explained in 'Two-way transparency', *Aust Prescr* 2005;28:103.

\* 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.emea.eu](http://www.emea.eu)).

## Answers to self-test questions

- |          |          |          |          |
|----------|----------|----------|----------|
| 1. False | 3. False | 5. False | 7. True  |
| 2. True  | 4. True  | 6. True  | 8. False |

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