

- CSL will not release EpiPen with a shelf-life of less than 13 months and in most cases it will be considerably more. Stock released since September 2005 will not expire for 17 months.

Letters explaining these changes were sent by CSL to doctors (general practitioners, immunologists, allergists, paediatricians and respiratory physicians), pharmacies and wholesalers.

## 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.

### Anecortave acetate

Retaane (Alcon)

vials containing 15 mg/0.5 mL suspension

Approved indication: macular degeneration

Australian Medicines Handbook section 11.7

Most people with age-related macular degeneration have the non-exudative (dry) form. The exudative (wet) form is less common, but is more likely to cause blindness. Blood vessels grow through defects in the basement membrane of the retina then leak. This leakage causes loss of vision and scarring. The vessels can be treated with photocoagulation or, in patients with classical subfoveal choroidal neovascularisation, photodynamic therapy with verteporfin.

As the exudative form involves neovascularisation, it is possible which inhibiting angiogenesis will stop the disease progressing. Anecortave acetate is a molecule, structurally related to cortisol, which inhibits the proteases needed for blood vessel growth. Injecting the depot formulation through a cannula into the posterior juxtасleral area can stabilise the condition for several months. If indicated, the injection can be repeated six months later.

A clinical trial randomised 128 patients to receive anecortave (3 mg, 15 mg or 30 mg) or a placebo. Most of these patients with wet age-related macular degeneration had predominantly classic lesions. After six months there was a significant difference in the size of the lesions in patients given 15 mg anecortave. Although this difference was not statistically significant after 12 months, there was a significant difference in visual acuity. Patients given 15 mg anecortave were more likely to have stable vision and less likely to have severe loss of vision than patients given placebo. Efficacy seems greater in the patients with predominantly classic lesions.<sup>1</sup> The advantage of anecortave over placebo remained for those patients still in the study after 24 months.<sup>2</sup>

During the study approximately 41% of patients dropped out, mainly because of disease progression.<sup>1</sup> Adverse events reported during clinical trials include eye pain, hyperaemia, cataract, reduced intraocular pressure and ptosis.

The product information contains summary data from phase II trials comparing anecortave with verteporfin and photodynamic therapy. One trial gave patients anecortave or placebo 5–8 days after photodynamic therapy with verteporfin. Anecortave did not have a statistically significant advantage over placebo. The other trial has now been published. It randomised 263 patients with predominantly classic lesions to receive anecortave and 267 to receive photodynamic therapy with verteporfin. After 12 months, 45% of the anecortave group and 49% of the photodynamic therapy group had lost less than three lines of vision on the trial's visual acuity chart. Although the trial was designed to show that anecortave was not inferior, non-inferiority could not be confirmed.<sup>3</sup>

**T T** manufacturer provided some data

### References

1. The Anecortave Acetate Clinical Study Group. Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration. *Ophthalmology* 2003;110:2372-85.
2. Schmidt-Erfurth U, Michels S, Michels R, Aue A. Anecortave acetate for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Eur J Ophthalmol* 2005;15:482-5.
3. Slakter JS, Bochow T, D'Amico DJ, Marks B, Jerdan J, Sullivan EK. Anecortave acetate (15 milligrams) versus photodynamic therapy for treatment of subfoveal neovascularization in age-related macular degeneration. *Ophthalmology* 2006;113:3-13.

### Erlotinib

Tarceva (Roche)

25 mg, 100 mg and 150 mg tablets

Approved indication: non-small cell lung cancer

Australian Medicines Handbook section 14.3.9

In some cancers there is overexpression of epidermal growth factor receptors. These receptors are linked to tyrosine kinase and increased tyrosine kinase activity is associated with angiogenesis and tumour progression. This enzyme is therefore a target for drug therapy (see 'Angiogenesis inhibitors in cancer' *Aust Prescr* 2006;29:9–15).

Erlotinib inhibits the tyrosine kinase associated with epidermal growth factor receptors. It is uncertain what effect it has on other tyrosine kinase enzymes.

As epidermal growth factor receptors are present in some lung cancer cells, erlotinib has been studied in patients whose cancers have progressed despite chemotherapy. In one trial seven of 57 patients who took erlotinib daily had a complete or partial response.<sup>1</sup> Erlotinib was then used in a double-blind placebo-controlled study of 731 patients with stage IIIB or IV non-small cell lung cancer which had previously been treated with chemotherapy. Less than 1% of the placebo group responded compared with 8.9% of the erlotinib group. Although erlotinib improved survival, the patients only lived for a median of 6.7 months while those in the placebo group survived for 4.7 months.<sup>2</sup>

During the double-blind trial 76% of the patients given erlotinib developed a rash. This required some people to reduce their dose. Other adverse effects with a frequency greater than placebo included stomatitis, infection, diarrhoea, anorexia and ocular toxicity.<sup>2</sup>

The bioavailability of erlotinib is greatly increased by food so the tablets should be taken at least one hour before or two hours after meals. Erlotinib is metabolised mainly by cytochrome P450 3A4 so there is a potential for interactions with drugs that inhibit or induce this enzyme. Caution is needed if the patient is taking warfarin. The half-life of erlotinib is 36 hours, but its clearance may be increased in smokers. No pharmacokinetic data are available on the use of erlotinib in patients with liver metastases.

The role of erlotinib still requires clarification. There is a possibility that patients who develop a rash survive longer<sup>1</sup> and there is debate about the efficacy of erlotinib in patients whose tumours do not overexpress epidermal growth factor receptors. There is no benefit in giving erlotinib with chemotherapy so its use is restricted to patients whose locally advanced or metastatic non-small cell lung cancer progresses after chemotherapy. Whether erlotinib has an overall advantage over gefitinib, another tyrosine kinase inhibitor with the same indication, is currently uncertain.

**T T T** manufacturer provided all requested information

## References \* †

1. Perez-Soler R, Chachoua A, Hammond LA, Rowinsky EK, Huberman M, Karp D, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol* 2004;22:3238-47.
2. Shepherd FA, Pereira JR, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-32.

## Lanthanum carbonate hydrate

Fosrenol (Orphan)

500 mg, 750 mg and 1000 mg chewable tablets

Approved indication: hyperphosphataemia in chronic renal failure

Australian Medicines Handbook section 7.7

Patients being treated with continuous ambulatory peritoneal dialysis or haemodialysis for chronic renal failure are at risk of hyperphosphataemia. High phosphorus concentrations are associated with increased mortality. To try and control hyperphosphataemia patients may be given binding agents such as calcium carbonate. These bind to phosphate in the gut to reduce its absorption.

Lanthanum is a rare earth element which can bind phosphate. The tablets of lanthanum carbonate hydrate dissociate in the acid environment of the upper gastrointestinal tract to release lanthanum ions. These ions bind with dietary phosphate to form lanthanum phosphate. As this compound is insoluble, phosphate absorption is reduced. The dose is adjusted every 2–3 weeks until the serum phosphate concentration is controlled. Most patients will require a total daily dose of 1500–3000 mg. The tablets are chewed three times a day with meals.

A six-week double-blind study compared lanthanum to placebo in 145 patients with end-stage renal disease and a serum phosphorus of at least 1.8 mmol/L. There was a dose-related reduction in serum phosphorus within two weeks of starting therapy.<sup>1</sup>

Another placebo-controlled trial enrolled 163 patients having haemodialysis. After a washout period and a dose-titration period, 94 patients were entered into a double-blind phase. This maintenance phase lasted for four weeks. At the end of this phase the serum phosphorus concentration in patients given placebo was similar to the concentration at the end of the washout period. The patients who continued lanthanum during the maintenance phase retained control of their phosphorus concentrations. At the end of the study their mean concentration was 1.92 mmol/L compared with 2.53 mmol/L in the placebo group.<sup>2</sup>

Comparative studies with other phosphate binders are limited. One study compared the effects of lanthanum carbonate and calcium carbonate on the development of renal osteodystrophy in 98 patients.<sup>3</sup> After one year 15% of the patients given lanthanum had normal bone histology compared with only 3% of the patients given calcium carbonate. Both binders controlled the phosphorus concentration.

Lanthanum is less likely to cause hypercalcaemia than calcium-based binders, but it may have more gastrointestinal adverse effects such as diarrhoea, nausea and vomiting. Although only a little lanthanum is absorbed it is distributed into bone.

Lanthanum is only slowly released (half-life greater than 26 weeks) and its long-term effects are unknown. Patients should not take lanthanum for more than two years.

Although lanthanum probably has advantages over calcium-based binders, so may sevelamer hydrochloride, another recently approved phosphate binder. There appear to be no published comparative trials of lanthanum and sevelamer. These drugs are more expensive than calcium carbonate and it is uncertain if their benefits outweigh their higher price.

**T** **T** manufacturer provided some data

## References

1. Finn WF, Joy MS, Hladik G. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. *Clin Nephrol* 2004;62:193-201.
2. Joy MS, Finn WF. Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. *Am J Kidney Dis* 2003;42:96-107.
3. D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S, et al. A multicenter study on the effects of lanthanum carbonate and calcium carbonate on renal bone disease in dialysis patients. *Kidney Int* 2003;63(Suppl 85):S73-S78.

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 Agency for the Evaluation of Medicinal Products ([www.emea.eu.int](http://www.emea.eu.int))

## Answers to self-test questions

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

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