

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.

Palifermin

Kepivance (Amgen)

vials containing 6.25 mg as lyophilised powder for reconstitution

Approved indication: oral mucositis

Australian Medicines Handbook section 14.5.2

Many patients who are treated with high doses of chemotherapy or radiation, particularly for head and neck cancers, develop oral mucositis. This can be very painful and in severe cases the patient may be unable to swallow. Mucositis increases the risk of the patient developing serious infections.

If mucositis is the result of damage to the oral tissues, then it could be ameliorated by giving growth factors. Palifermin is a genetically engineered form of keratinocyte growth factor which stimulates the development of epithelial cells.

The efficacy of palifermin has been assessed in 212 patients having chemotherapy and radiation before stem cell transplantation for haematological malignancies. These patients were given a daily intravenous injection of palifermin or placebo for three days before their treatment. They received three more doses following transplantation. Significant mucositis developed in 98% of the placebo group, but only in 63% of the patients given palifermin. It lasted six days with palifermin, but nine days with placebo. This probably contributed to the reduced use of opioid analgesics with palifermin. Although 75% of the patients given palifermin developed febrile neutropenia, this was significantly less than the 92% in the placebo group.¹

Adverse effects which occur more frequently in patients given palifermin include rash, itching, erythema and altered taste and other sensations in the mouth. Patients may also complain of arthralgia, paraesthesia, oedema and cough. There is a theoretical risk that palifermin could promote cataract formation.

Animal studies suggest that palifermin can enhance the growth of epithelial tumours. As safety and efficacy have not been shown in other tumours, palifermin is currently only approved for patients with haematological malignancies receiving myelotoxic therapy requiring stem cell support.

 manufacturer declined to supply data

Reference [†]

1. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004;351:2590-8.

Quinagolide

Norprolac (Ferring)

25 microgram and 50 microgram tablets

Approved indication: hyperprolactinaemia

Australian Medicines Handbook section 16.2.1

The secretion of prolactin from the anterior pituitary is inhibited by dopamine. Dopamine agonists have therefore been used to treat hyperprolactinaemia, a condition which has several possible causes including prolactinomas in the pituitary.

Quinagolide is a selective agonist at the dopamine D₂ receptor. It has been approved for the treatment of idiopathic hyperprolactinaemia and prolactin secreting pituitary tumours.

Patients take quinagolide once a day. The drug is well absorbed but there is extensive first-pass metabolism.

Prolactin concentrations start to fall within two hours of a dose and are suppressed for 24 hours. Most of the drug is metabolised with the metabolites being excreted in the faeces and urine. Therefore, impaired hepatic or renal function are contraindications to quinagolide.

As quinagolide has been available overseas for several years, long-term data are available. One study reported on a group of 40 patients treated for a mean of 32 months. The serum prolactin fell in all patients and the tumour size was reduced in 55% of the patients with microadenomas and 75% of the patients with macroadenomas. Hyperprolactinaemia can be a cause of infertility, but 10 of the 38 women in the study became pregnant while taking quinagolide.¹

Most of the early comparative studies of quinagolide used bromocriptine. A study of 41 women found both drugs significantly reduced serum prolactin within eight weeks. Prolactin concentrations normalised in 81% of those given quinagolide and 70% of those given bromocriptine. Tolerability was higher in the women given quinagolide.² Another study showed that 39% of patients with prolactinomas that were resistant to treatment with bromocriptine responded to quinagolide.³

Bromocriptine is no longer first-line therapy because treatment with cabergoline is more effective. Quinagolide has therefore been compared with cabergoline. In one small study patients took one of the drugs for 12 weeks then stopped. When their hyperprolactinaemia returned they took the other drug for 12 weeks. Although only nine patients completed the study,

there were significant differences in the duration of efficacy and tolerability favouring cabergoline.⁴ A similar study stopped treating 39 patients with quinagolide after a year then, when their hyperprolactinaemia returned, treated them with cabergoline for a year. Cabergoline had a greater effect on tumour size and was better tolerated.⁵

The adverse effects of quinagolide include nausea, vomiting, headache and dizziness. Some of these symptoms improve after a few days of treatment. It is therefore recommended that quinagolide is taken with food at night and that treatment is introduced gradually. In some cases the dopaminergic action of quinagolide may cause an acute psychosis.

The once-daily dose and better tolerability give quinagolide an advantage over bromocriptine. Any differences between quinagolide and cabergoline are less clear. Cabergoline needs to be given less frequently and if the patient only needs one dose a week, a month's treatment will be cheaper than daily treatment with quinagolide.

 manufacturer provided all requested information

References

1. Schultz PN, Ginsberg L, McCutcheon IE, Samaan N, Leavens M, Gagel RF. Quinagolide in the management of prolactinoma. *Pituitary* 2000;3:239-49.
2. van der Heijden PF, de Wit W, Brownell J, Schoemaker J, Rolland R. CV 205-502, a new dopamine agonist, versus bromocriptine in the treatment of hyperprolactinaemia. *Eur J Obstet Gynecol Reprod Biol* 1991;40:111-18.
3. Morange I, Barlier A, Pellegrini I, Brue T, Enjalbert A, Jaquet P. Prolactinomas resistant to bromocriptine: long-term efficacy of quinagolide and outcome of pregnancy. *Eur J Endocrinol* 1996;135:413-20.
4. Giusti M, Porcella E, Carraro A, Cuttica M, Valenti S, Giordano G. A cross-over study with the two novel dopaminergic drugs cabergoline and quinagolide in hyperprolactinemic patients. *J Endocrinol Invest* 1994;17:51-7.
5. Di Sarno A, Landi ML, Marzullo P, Di Somma C, Pivonello R, Cerbone G, et al. The effect of quinagolide and cabergoline, two selective dopamine receptor type 2 agonists, in the treatment of prolactinomas. *Clin Endocrinol* 2000;53:53-60.

Sevelamer hydrochloride

Renagel (Genzyme)

800 mg tablets

Approved indication: hyperphosphataemia in chronic renal disease

Australian Medicines Handbook section 7.8

Patients with end-stage renal disease are at risk of hyperphosphataemia. This is associated with hyperparathyroidism, bone resorption and increased mortality. One strategy to control hyperphosphataemia is to reduce the absorption of phosphate from the gut. This can be achieved with a binding agent such as calcium acetate.

Sevelamer is a polymer which binds phosphates in the gut. The complex is not absorbed, so serum concentrations of phosphate should fall. Patients take tablets with every meal, at a dose determined by the serum phosphorus. The target concentration is 1.78 mmol/L or less.

Several studies have compared sevelamer with calcium acetate. In one study 83 patients having haemodialysis took calcium acetate or sevelamer for eight weeks, then after a two-week washout, swapped to the other drug for eight weeks. The effects on serum phosphate were similar, but patients taking calcium acetate were more prone to develop hypercalcaemia.¹

Another comparative study found that although patients given calcium acetate were more likely to develop hypercalcaemia, they were also more likely to reach the target phosphate concentration. This study concluded that calcium acetate should remain the treatment of choice, because of its significantly lower cost.²

The cost-benefit assessment may be changed if the results of an unpublished long-term study are confirmed. This study of more than 2000 patients found reduced mortality in elderly people and patients treated with sevelamer for more than two years. Although the benefit was significant in these sub-groups, there was no significant overall advantage over calcium-based phosphate binders.³

Although sevelamer causes less hypercalcaemia, it may cause more dyspepsia than calcium acetate. In a pooled analysis of 384 patients, 58 discontinued sevelamer because of adverse events. These included dyspepsia, abdominal pain, diarrhoea, nausea and vomiting. As sevelamer binds bile acids there is a theoretical possibility it could reduce the absorption of fat soluble vitamins.

Sevelamer reduces concentrations of low density lipoprotein cholesterol. This could help to prevent cardiovascular calcification in patients having haemodialysis, however this strategy is likely to be more expensive than giving calcium acetate and a lipid-lowering drug.² Until the long-term effects of sevelamer are clearer it seems likely that its use will be determined by its cost.

 manufacturer declined to supply data

References * †

1. Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. *Am J Kidney Dis* 1999;33:694-701.
2. Qunibi WY, Hootkins RE, McDowell LL, Meyer MS, Simon M, Garza RO, et al. Treatment of hyperphosphatemia in hemodialysis patients: the Calcium Acetate Renagel Evaluation (CARE Study). *Kidney Int* 2004;65:1914-26.
3. <http://www.genzyme.com/corp/investors/GENZ%20PR-072805.asp>

Strontium ranelate

Protos (Servier)

sachets containing 2 g granules for oral suspension

Approved indication: postmenopausal osteoporosis

Australian Medicines Handbook section 10.3

Strontium is an element which was used in the past to treat osteoporosis. It fell out of use because it was associated with defects in bone mineralisation. Strontium ranelate aims to overcome the problems associated with strontium.

Patients take 2 g of granules in water. As the slow absorption is reduced by food, the dose should be taken at bedtime at least two hours after eating. Binding in the gut can reduce the absorption of some antibiotics. Tetracyclines and quinolones should therefore not be taken with strontium ranelate.

When the molecule dissociates, the strontium is taken into bone. It is thought to stimulate osteoblasts to make bone and to decrease the resorption of bone by osteoclasts. Strontium is slowly released from bone and excreted by the gut and kidney. Clearance is reduced by renal disease. The half-life of strontium is approximately 60 hours.

Strontium ranelate was studied in 353 women with postmenopausal vertebral osteoporosis and a history of at least one vertebral fracture. These women were randomised to take different doses of strontium ranelate or a placebo for two years. They also took calcium and vitamin D. There was a rise in alkaline phosphatase activity and a dose-dependent increase in lumbar bone density in the women who took strontium ranelate.¹

A subsequent trial enrolled 1649 postmenopausal women with a history of osteoporosis and at least one vertebral fracture. These women took calcium and vitamin D with either 2 g of strontium ranelate or a daily placebo. After three years the bone mineral density of the lumbar spine had increased by 6.8% in the women taking strontium ranelate, but decreased by 1.3% in the placebo group. New vertebral fractures appeared on the X-rays of 20.9% of those taking strontium ranelate and 32.8% of those taking placebo. Symptomatic vertebral fractures occurred in 11.3% of the strontium group and 17.4% of the placebo group – a small, but statistically significant difference.²

Another study looked at the effect of strontium ranelate on non-vertebral fractures in 4932 elderly women with reduced bone density. Strontium increased bone density and over three years there was a 16% reduction in the relative risk of fractures. The absolute difference in fractures was small, with a cumulative incidence of 12.9% in the placebo group and 11.2% in the women taking strontium. There was only a 0.5% overall reduction in hip fractures over three years.³

Common adverse effects of strontium ranelate include headache, nausea and diarrhoea. Although the incidence is less than 1%, there is a higher risk of venous thromboembolism in

patients taking strontium ranelate. Neurological problems such as altered consciousness or seizures occurred more frequently with strontium in placebo-controlled trials.

While serum calcium may fall during treatment, strontium can interfere with some of the laboratory assays used to measure calcium concentrations. At present there are limited histomorphometric data to assess the mineralisation of bone during treatment.

Based on the trial of the 2 g dose, nine patients, with osteoporosis and a history of fracture, would need to take strontium ranelate, calcium and vitamin D for three years to prevent one radiological fracture of a vertebra.² The reduction in the risk of vertebral fracture is similar to that seen with bisphosphonates, but the drugs do not seem to have been directly compared in published trials.

T T manufacturer provided some data

References [†]

1. Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis – a 2-year randomized placebo controlled trial. *J Clin Endocrinol Metab* 2002;87:2060-6.
2. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350:459-68.
3. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in post-menopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90:2816-22.

NEW FORMULATION

Tramadol hydrochloride

Tramal oral drops (CSL)

10mL and 30 mL bottles containing 100 mg/mL

(Tramal oral drops are not approved for use in children)

See also NPS RADAR review at www.npsradar.org.au

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).

† 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)