

## Dental notes

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### Cardiac effects of non-cardiac drugs

Dentists have traditionally been concerned about the potential risk of cardiac effects from the vasoconstrictor, either adrenaline or octapresin, in dental local anaesthetics. However, the evidence shows that there is minimal effect from either of these drugs in appropriate dosage. There is a much greater

effect from endogenous production of adrenaline if the dental procedure is painful.

Non-steroidal anti-inflammatory drugs are widely used for dental pain and dentists should be aware of the potential cardiac adverse effects, particularly with long-term use of these drugs. The concept of using these very effective drugs for the shortest time possible at the lowest effective dose is an excellent guiding principle for all patients. Concurrent use of other analgesics, as well as correct diagnosis and timely and effective provision of dental treatment, can go a long way in diminishing the long-term adverse effects of these drugs.

## 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.

### Canakinumab

Ilaris (Novartis)

vials containing 150 mg lyophilised powder for reconstitution  
Approved indication: cryopyrin-associated periodic syndromes  
Australian Medicines Handbook section 15.2.2

Cryopyrin-associated periodic syndromes are a group of rare but often severe inflammatory disorders including familial cold autoinflammatory syndrome or familial cold urticaria, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease. These disorders are associated with mutations in the gene that encodes cryopyrin, a protein involved in the regulation of interleukin-1 $\beta$ . The defect results in over-production of interleukin-1 $\beta$  and leads to inflammation that can affect the skin, eyes, bones, joints and meninges. Patients may also experience severe fatigue, fever, myalgia, chronic anaemia and learning difficulties.

Currently there are no approved treatments for cryopyrin-associated periodic syndromes in Australia, but colchicine, corticosteroids and sometimes anakinra (Aust Prescr 2004;27:160-1) have been used in these patients. Canakinumab is a human monoclonal antibody that specifically binds to interleukin-1 $\beta$ , neutralising its activity. After subcutaneous administration, peak serum concentrations are reached after 7 days in adults and between 2 and 7 days in children. The average terminal half-life is 26 days in adults and between 22.9 and 25.7 days in children.

In an early study, four patients responded to one intravenous dose of canakinumab 10 mg/kg – urticarial rashes disappeared within 24 hours and patients experienced a complete response by one week. The median time until re-dosing after disease flare was approximately 26 weeks.<sup>1</sup>

In a larger 48-week trial, 34 of 35 patients (aged 4–75 years) responded to a single open-label subcutaneous dose of canakinumab 150 mg (or 2 mg/kg for those under 40 kg) within a month. After 8 weeks, patients who had responded were randomised to receive either canakinumab or placebo (at 8-week intervals) for a further 24 weeks. The 15 patients given canakinumab stayed in remission, whereas 13 of the 16 patients given placebo relapsed. Disease activity seemed to correlate with C-reactive protein and serum amyloid A concentrations – both were elevated in the placebo group but normalised in the canakinumab group. After 32 weeks, 6 of the 15 patients in the canakinumab group said their symptoms had completely gone compared to none of the patients in the placebo group. In a third phase of the trial, 31 patients were given open-label canakinumab (at least 2 doses over 16 weeks). Of the 29 who completed treatment, 28 people were in remission.<sup>2</sup>

As canakinumab suppresses the immune system, infections are a risk. The most frequently reported adverse reactions with canakinumab were upper respiratory tract infections and pharyngitis (up to 33.3%). Also, there were more suspected infections with canakinumab than with placebo (10 patients vs 4 patients).<sup>2</sup> Two patients given canakinumab had serious adverse events – one had urinary tract infection requiring hospitalisation and the other developed vertigo with acute closed-angle glaucoma. Both patients discontinued treatment.<sup>2</sup>

Because of the risk of infections, patients should be tested for latent and active tuberculosis before starting treatment and caution is urged in patients with a history of recurring infections. Canakinumab should not be started or continued in patients with active infection requiring medical treatment. Concomitant use of tumour necrosis factor inhibitors or live vaccines is not

recommended with canakinumab. Patients should complete all appropriate vaccinations before starting treatment.

As cytochrome P450 enzymes can be suppressed by cytokines such as interleukin 1 $\beta$ , canakinumab may reverse this and affect the metabolism of some drugs. Dose adjustment for drugs with a narrow therapeutic index may be necessary.

Due to lack of clinical data, canakinumab is not recommended during pregnancy and lactation or in children under 4 years of age. So far antibodies to canakinumab have not been detected in recipients of the drug.

Canakinumab is the first interleukin-1 blocker to be approved for cryopyrin-associated periodic syndromes in Australia. A subcutaneous injection every eight weeks appeared to be effective in reducing inflammatory symptoms, although the pivotal trial was very small. Prescribers need to be vigilant for infections in patients receiving canakinumab.

**T** manufacturer provided the product information

## References \*†

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2. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med* 2009;360:2416-25.

## Eltrombopag olamine

Revolade (GlaxoSmithKline)

25 mg and 50 mg tablets

Approved indication: idiopathic thrombocytopenic purpura

Australian Medicines Handbook Appendix A

Chronic idiopathic thrombocytopenic purpura is an immune condition caused by autoantibodies which bind to platelets. This leads to increased destruction of platelets, putting patients at risk of bleeding. The condition tends to have episodes of relapse and remission. If it cannot be controlled by corticosteroids, immunoglobulins or splenectomy, a drug such as romiplostim can be given to stimulate platelet production.

Like romiplostim, eltrombopag increases platelet production by interacting with the thrombopoietin receptor. Whereas romiplostim is a peptide which has to be injected, eltrombopag is a small non-peptide molecule which can be given orally. It should not be taken within four hours of antacids, dairy products or mineral supplements as these reduce absorption. Higher concentrations are reached in East Asian patients so a lower starting dose (25 mg) is recommended. Most of the dose is metabolised and most of the metabolites are excreted in the faeces. The elimination half-life in patients is 26–35 hours.

Eltrombopag increases the concentrations of rosuvastatin and may interact with other HMGCoA reductase inhibitors.

A dose-ranging study randomised 118 patients to take a daily dose of eltrombopag 30 mg, 50 mg or 75 mg or placebo for up to six weeks. These patients had platelet counts below  $30 \times 10^9/L$  despite treatment. The trial end point was a platelet count of at least  $50 \times 10^9/L$ . This was reached by 28% of the patients given eltrombopag 30 mg, 70% of those given 50 mg and 81% of those given 75 mg. Only 11% of the placebo group reached the end point. The significant advantage of the 50 mg and 75 mg doses led to the trial being stopped.<sup>1</sup>

A starting dose of eltrombopag 50 mg was used in a subsequent phase III trial in patients who remained thrombocytopenic despite having had at least one previous therapy. The dose was increased to 75 mg if patients did not achieve a platelet count of  $50 \times 10^9/L$  after three weeks. Compared to the 38 patients randomised to placebo, there was a significantly greater response in the 76 patients randomised to eltrombopag. The target platelet count was achieved at six weeks by 59% of the eltrombopag group, but by only 16% of the placebo group.<sup>2</sup>

To assess the efficacy of longer-term treatment, 135 patients with platelet counts below  $30 \times 10^9/L$  were randomised to receive eltrombopag 50 mg for six months. The dose could be adjusted to 25 mg or 75 mg as needed. Another 62 patients were randomised to take a daily placebo. After six months of treatment 79% of the eltrombopag group, but only 28% of the placebo group, had achieved a platelet count of  $50\text{--}400 \times 10^9/L$  on at least one occasion. The response to eltrombopag tended to be maintained. Significantly more of the patients taking eltrombopag were able to reduce their other treatments.<sup>3</sup>

Diarrhoea, nausea and vomiting were common adverse events in the clinical trials. Eltrombopag is potentially hepatotoxic. A study of patients with liver disease had to be stopped because of adverse events such as portal vein thrombosis. Liver function should be tested before treatment, then every two weeks until the dose is stable and then monthly.

Cataracts were reported in animal studies of eltrombopag. An eye examination is therefore recommended for patients before and during treatment.

A potential hazard of a rapid rise in platelet count is thrombosis. In clinical trials, thromboembolic events occurred in 3.8% of patients.

Eltrombopag may increase the risk of bone marrow fibrosis. This is one possible cause for a loss of response to treatment.

The effect of eltrombopag wears off quickly. Within two weeks the patients' platelet counts will fall back to baseline levels or below. There may be an increased risk of bleeding at this time.

Although treatment with eltrombopag reduces bleeding it does not completely prevent it. During the six month study 19%

of the patients taking eltrombopag and 31% of those taking placebo had bleeding as an adverse effect of treatment. This bleeding was serious in less than 1% of the eltrombopag group and 7% of the placebo group.<sup>3</sup>

Apart from oral administration, it is not known if eltrombopag has advantages over romiplostim. Until more is known about the long-term effects of stimulating the thrombopoietin receptor, the drug will be reserved for adult patients with an unsatisfactory response to other treatments.

**T** manufacturer provided the AusPAR

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3. Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011;377:393-402.

## Sapropterin dihydrochloride

Kuvan (Merck Serono)

100 mg soluble tablets

Approved indication: hyperphenylalaninaemia

Australian Medicines Handbook Appendix A

The amino acid phenylalanine is normally metabolised by phenylalanine hydroxylase to form tyrosine. This metabolism involves a co-enzyme called tetrahydrobiopterin (BH4). Inborn errors of metabolism or a deficiency of BH4 result in the accumulation of phenylalanine which leads to intellectual disability. There are many possible mutations. Phenylketonuria is the most common of the hyperphenylalaninaemias.

Patients with phenylketonuria have to follow a diet low in phenylalanine. The diet can be difficult to adhere to, so there has been research into other approaches. Supplementing BH4 may help to offset the abnormal metabolism. In a study of 31 patients with mild hyperphenylalaninaemia/phenylketonuria, giving BH4, after a loading dose of phenylalanine, reduced the concentration of phenylalanine in the blood.<sup>1</sup>

Sapropterin is a synthetic form of BH4. Although its bioavailability is probably low, it can be given by mouth. Taking the daily dose with food improves absorption.

An open-label trial of sapropterin treated 485 patients with phenylketonuria for eight days. The concentrations of phenylalanine in the blood fell by at least 30% in 96 of the patients.<sup>2</sup> A group of these responders was later enrolled in a double-blind trial.

In the double-blind trial the 89 patients were randomised to take sapropterin or a placebo for six weeks. Both groups had similar blood concentrations of phenylalanine in the two weeks before drug treatment began. These concentrations then fell by at least 30% in 44% of the sapropterin group, but in only 9% of the placebo group. The mean change from the baseline concentration was a fall of 235.9 micromol/L in the treatment group and a rise of 2.9 micromol/L in the control group.<sup>3</sup>

Although the trial included a few children, another study looked specifically at children who were 4–12 years old. In the first part of the trial the children were given an eight-day course of sapropterin. Those who experienced at least a 30% reduction in phenylalanine concentrations, to below 300 micromol/L, were eligible for the next part of the study. Following a washout period of at least one week, 46 responders were randomised to take sapropterin or a placebo for 10 weeks. After three weeks there was a significant difference in the blood concentrations of phenylalanine in the treatment and control groups. The mean concentrations fell in the 33 children who took sapropterin, but were unchanged with placebo. From the third week of the study, depending on the blood concentrations, supplements of phenylalanine were added to the children's diet. The amount could be increased or decreased every two weeks. At the end of the study the children given sapropterin had been able to tolerate significantly more supplements than the placebo group.<sup>4</sup>

The placebo-controlled trials were short and few differences emerged in adverse events. The events which were more frequent with sapropterin than with placebo included rhinorrhoea, pharyngolaryngeal pain, diarrhoea and headache. Nobody withdrew from the trials because of adverse reactions.<sup>3,4</sup> There were no studies of drug interactions, but sapropterin could interact with drugs such as methotrexate, which inhibit folate metabolism, and nitric oxide-mediated vasodilators such as sildenafil. There may be neurological adverse effects if the patient takes sapropterin and levodopa.

Only a minority of patients with phenylketonuria or BH4 deficiency will have a significant response to treatment with sapropterin. The only way to identify these patients is with a therapeutic trial. If there is no change in the blood concentration of phenylalanine after one month, treatment should be stopped. Sapropterin will not be effective enough to allow many patients to ease their dietary restrictions. A low phenylalanine diet should therefore continue during treatment with regular monitoring of blood concentrations.

**T T** manufacturer provided additional useful information

## References \*†

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- Burton BK, Grange DK, Milanowski A, Vockley G, Feillet F, Crombez EA, et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study. *J Inher Metab Dis* 2007;30:700-07.
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## Zonisamide

Zonegran (Sci Gen)

25 mg, 50 mg and 100 mg capsules

Approved indication: partial seizures

Australian Medicines Handbook section 16.1.3

Many adults with refractory epilepsy have partial seizures which may or may not become generalised. When monotherapy fails, it can be difficult to decide which adjunctive treatment will help the patient. Zonisamide adds to the list of drugs such as gabapentin, lamotrigine, tiagabine and topiramate, which can be used as add-on therapy. While it is a new drug in Australia, zonisamide has been available for many years in Japan.

Zonisamide is a sulfonamide, but its mechanism of action in epilepsy is uncertain. It may stabilise neuronal membranes by blocking sodium and calcium channels. Zonisamide is also a weak inhibitor of carbonic anhydrase.

The capsules are well absorbed and food does not affect bioavailability. Zonisamide has a long half-life so it takes up to 14 days for its concentration to reach a steady state. The dose should therefore not be increased at intervals of less than one week. Treatment begins with twice-daily doses, but patients can switch to once daily after the dose has been titrated to an effective level. Most of the dose is excreted in the urine as unchanged drug and metabolites, so clearance falls with declining renal function. Doses may therefore need to be titrated more slowly in patients with renal or hepatic impairment. The metabolism of zonisamide includes cytochrome P450 3A4 so there is a potential for interactions with other drugs acting on this enzyme system. Clearance is increased by phenytoin, sodium valproate and carbamazepine. Zonisamide may possibly interact with carbonic anhydrase inhibitors such as topiramate.

A study in the USA compared zonisamide with placebo in 203 patients with refractory partial seizures. Different regimens were used to titrate the dose, but all patients randomised to take zonisamide were on 400 mg daily from the eighth week of the study. Patients continued their usual antiepileptic drugs.

In the month before randomisation the median frequency of partial seizures was 13 in the placebo group and 11–13 in the zonisamide groups. During weeks 8–12 of the study, the median frequency of all seizures was reduced by 9% in the placebo group and by 40.5% in the zonisamide group.<sup>1</sup>

Another American study randomised 152 patients to add zonisamide or a placebo to their usual treatment for 12 weeks. The dose of zonisamide was titrated over four weeks to 400–600 mg daily. The baseline median frequency of seizures was approximately nine per month, but there was a 25.5% reduction after patients took zonisamide. In the placebo group there was a 6.6% increase in seizure frequency.<sup>2</sup>

In a European study 347 patients added a placebo or one of three doses of zonisamide to their usual therapy. The fixed-dose phase of the trial lasted for 18 weeks. During this phase, seizure frequency reduced by 17.4% in the placebo group and by 38.5% in patients taking zonisamide 300 mg daily. The efficacy of zonisamide 100 mg was not statistically different from placebo. While the median reduction in seizure frequency with zonisamide 500 mg was 46.1%, the response probably does not greatly increase above a daily dose of 400 mg.<sup>3</sup>


Frequent adverse effects with zonisamide include somnolence, dizziness and anorexia. Some patients lost weight during the trials.<sup>1,3</sup> Adverse neurological events include ataxia, nystagmus, agitation and altered cognitive function. Driving skills may be impaired.

Zonisamide can cause rashes, including Stevens-Johnson syndrome. The product information states that it is contraindicated if the patient has an allergy to sulfonamides.

Prescribers may need to consider monitoring renal function as zonisamide has been associated with increases in urea and creatinine concentrations. Patients should be advised to maintain their hydration in warmer weather as oligohydrosis and hyperthermia have been reported (mainly in children). Early development of the drug in the USA was halted because 3.5% of patients developed kidney stones.<sup>1</sup>

Zonisamide is teratogenic in animals and is not approved for use in children.

Although zonisamide reduces seizure frequency more than placebo, few patients will become free of seizures. Depending on the dose, a greater than 50% reduction in the frequency of all seizures is achieved by 30–53% of patients.

 manufacturer provided clinical evaluation

## References \*†

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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/pmeds/auspar.htm](http://www.tga.gov.au/pmeds/auspar.htm))



To find out about recent additions to the Pharmaceutical Benefits Scheme, see the April issue of NPS RADAR. It reviews the evidence and place in therapy for:

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### Answers to self-test questions

1. True            3. True
2. False          4. False

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