

In Brief

A digest of news items about NPS RADAR, new drugs and changes to PBS listings.

Paracetamol with caffeine (Panadol Extra) available over the counter from pharmacies

Panadol Extra tablets (containing paracetamol 500 mg with caffeine 65 mg per tablet) became an S2 pharmacy-only medicine on 1 May 2010. Similar to paracetamol, this preparation is indicated for the temporary relief of pain and discomfort associated with a number of conditions.^{1,2} Paracetamol with caffeine is a new combination in Australia but has been available overseas for many years.³

Caffeine is claimed to enhance the efficacy of paracetamol.¹ However, peak plasma levels and extent of absorption are similar for paracetamol with caffeine and paracetamol alone.¹ Compared with paracetamol alone, a person taking the combination of paracetamol with caffeine may be more likely to experience adverse effects than to get improved analgesia.

The benefit of adding caffeine to paracetamol is uncertain

The extent to which caffeine improves the analgesic effect of paracetamol is uncertain and may not be clinically meaningful. Published trials have assessed the effect of combining caffeine with paracetamol compared with paracetamol alone in conditions including tension-type⁴ and non-migrainous headaches⁵, postoperative pain^{6,7}, uterine cramping⁶ and primary dysmenorrhoea.⁸

Trials were generally of poor quality and had conflicting results: some showed a small benefit, most did not. For example, a trial of 320 young women found that a single dose of paracetamol with caffeine provided more pain relief for primary dysmenorrhoea 2 hours post dose than paracetamol (mean difference in pain relief scores* 0.27, 95% confidence interval 0.03 to 0.52, P = 0.03) but it is unclear whether this is clinically meaningful.⁸

In addition, there is no evidence on the effect of repeat dosing, as only single doses were studied (2–4 hours post dose) in the trials.^{4–8}

Caffeine may cause adverse effects

The amount of caffeine that can be ingested per day from paracetamol with caffeine is between 65 mg (1 tablet) and 520 mg (8 tablets).¹ Even a small dose of 50 mg caffeine can cause tachycardia, anxiety and ectopic beats.⁹ Toxicity is normally seen at doses > 500 mg, but this depends on tolerance.⁹

Take into account dietary and other medicinal sources of caffeine: people may not be aware from the brand name that this preparation contains caffeine. Consider whether paracetamol with caffeine is necessary: it cannot be assumed that it will be tolerated in the same way as paracetamol alone.

Frequent and prolonged use may result in medication-overuse headache

Medication-overuse (rebound) headache may occur with prolonged and frequent use of medicines used for headache, including those containing paracetamol and caffeine.^{10,11}

Medication-overuse headache is the most prominent sign of withdrawal⁹ and over time may lead to an imperceptible dependence on analgesic drugs.¹⁰ It can be diagnosed only after abstinence from the drug for a week or more.¹⁰

Ask about pregnancy and breastfeeding

Pregnant women should not consume more than 200 mg caffeine per day, as this may increase the risk of spontaneous miscarriage.⁹ Consuming > 300 mg per day may also increase the risk of preterm delivery and foetal growth retardation.⁹

Caffeine is readily transferred to breast milk and young infants are poor metabolisers of caffeine.⁹ Infants who are breastfed by mothers consuming > 300 mg caffeine per day may become jittery and restless and experience sleep difficulties.⁹ No long-term adverse effects from consuming caffeine in breast milk have been documented.⁹

* Using a 5-point pain relief scale where 0 = none, 1 = a little, 2 = some, 3 = a lot and 4 = complete.

Counselling points for patients and carers

Caffeine is present in a variety of foods and beverages (Box 1) as well as in herbal, prescription and over-the-counter medicines.⁹

Advise people to take into account dietary and other medicinal sources of caffeine if paracetamol with caffeine is being taken, so that they do not consume more than the recommended maximum of 520 mg caffeine per day.¹²

Inform people about adverse effects that may occur with higher doses of caffeine, including toxic symptoms such as anxiety, insomnia, gastrointestinal symptoms, increased heart rate and blood pressure, diuresis and dehydration.⁹ People experiencing anxiety or stress may benefit from reducing their caffeine intake to < 210 mg per day.¹³

Advise against use for headache for more than 2–3 days per week to avoid medication-overuse headache.^{10,11} Encourage people to use a diary to monitor and record the frequency and severity of headaches and medicine use.

Warn people that paracetamol has many brands and is contained in other products such as cough and cold preparations. If the use of other paracetamol-containing preparations cannot be avoided, ensure that these are accounted for in the maximum dose of 4 g (8 tablets) paracetamol per day.

Box 1: Caffeine content of commonly consumed items compared with paracetamol with caffeine tablets¹³

Beverage/item	Container/size	Typical caffeine content
Coffee		
– Instant	250 mL cup	60–80 mg
– Percolated		60–120 mg
Tea	250 mL cup	10–50 mg
Coca Cola	375 mL can	48.75 mg
Energy drink	250 mL can	80 mg
Chocolate bar	100 g bar	20 mg
Paracetamol with caffeine	1 dose (= 2 tablets)	130 mg

References

1. GlaxoSmithKline Consumer Healthcare. Panadol Extra product information. 9 October 2009.
2. GlaxoSmithKline Consumer Healthcare. Panadol product information 1 May 2003.
3. Anonymous. *Prescrire International* 1997;6:90.
4. Migliardi JR, et al. *Clin Pharmacol Ther* 1994;56:576–86.
5. Ward N, et al. *Pain* 1991;44:151–5.
6. Laska EM, et al. *Clin Pharmacol Ther* 1983;33:498–509.
7. Winter L, et al. *Curr Ther Res* 1983;33:115–22.
8. Ali Z, et al. *Curr Med Res Opin* 2007;23:841–51.
9. Therapeutic Guidelines: Psychotropic. Version 6. Updated March 2010
10. Therapeutic Guidelines: Neurology. Version 5. Updated March 2010.
11. Australian Medicines Handbook 2010.
12. Medicines and Healthcare products Regulatory Agency. MHRA-UKPAR-Paracetamol Extra/Plus tablets PL16028/0141-2. London: MHRA, 2009. <http://www.mhra.gov.uk/home/groups/par/documents/websitesresources/con049106.pdf> (accessed 26 March 2010).
13. Food Standards Australia New Zealand. Fact sheet: caffeine. Canberra: FSANZ, 2010. <http://www.foodstandards.gov.au/scienceandeducation/factsheets/factsheets2010/caffeinejune2010.cfm> (accessed 29 June 2010).

Colchicine for acute gout: updated information about dosing and drug interactions

New evidence illustrates that low-dose colchicine is effective for acute gout, and highlights the risk of serious interactions with some commonly prescribed medicines.^{1,2}

Health professionals should be aware of:

- the revised dosing recommendations for colchicine in acute gout
- the need to avoid colchicine, or adjust the dose, in patients with renal or hepatic impairment and/or who are taking drugs that interact with colchicine (Box 1).

Existing concerns about colchicine dosing and toxicity

Vomiting and diarrhoea commonly occur when colchicine is repeatedly dosed at 1-hour or 2-hour intervals for acute gout.^{1,3} These are the first signs of colchicine toxicity, and may precede rare adverse effects, including muscle damage, neuropathy, multiple organ failure and bone marrow suppression.⁴ Patients with renal or hepatic impairment may be particularly susceptible to severe colchicine toxicity (Box 2).^{2,5–7}

Increasing awareness of toxicity led prescribing guidelines to recommend lower colchicine doses and extended dosing intervals.^{8–10} Case reports and expert opinion suggested that the treatment benefit could be maintained at lower colchicine doses, but no data from controlled trials were available until recently.^{1,11}

New evidence to support the use of low-dose colchicine in acute gout

Recent trial evidence demonstrates that low-dose colchicine (2 tablets followed by 1 tablet 1 hour later) is effective when prescribed within 12 hours of onset of an acute gout flare, with a low incidence of gastrointestinal adverse effects (Table 1).¹ A higher dose (2 tablets followed by 1 tablet every hour for 6 hours) offered no additional clinical benefit, but increased the risk of gastrointestinal toxicity. This study was conducted in the United States, where colchicine is available as 0.6 mg tablets rather than the 0.5 mg tablets available in Australia.

Table 1: Safety and efficacy of low-dose colchicine in acute gout¹

	High dose* (4.8 mg total; n = 52)	Low dose† (1.8 mg total; n = 74)	Placebo (n = 59)
Improved pain			
Patients with ≥ 50% reduction in pain after 24 hours	33%‡	38%‡	16%
Adverse effects			
Patients with nausea, vomiting and/or diarrhoea	77%§	26%	20%

* 1.2 mg initially followed by 0.6 mg every hour for 6 hours

† 1.2 mg initially followed by 0.6 mg 1 hour later

‡ Statistically significant difference compared with placebo

§ Statistically significant difference compared with placebo and low-dose colchicine

Drug interactions increase risk of colchicine toxicity

Concurrently prescribing colchicine and inhibitors of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) increases the potential for colchicine toxicity (Box 1).^{2,5} The US Food and Drug Administration reported that of 117 cases of fatal colchicine toxicity at therapeutic doses (≤ 2 mg/day), more than half occurred in patients who were taking clarithromycin at the same time.² However, a possible role for renal impairment or prolonged colchicine dosing cannot be excluded in these cases.

Fatal and non-fatal colchicine toxicity has occurred in patients taking colchicine and concomitant erythromycin, cyclosporin, statins and calcium-channel blockers, including verapamil and diltiazem.^{2,12}

Box 1: Common inhibitors of CYP3A4 and/or P-gp that may increase the risk of colchicine toxicity^{2,12-14}

Antiarrhythmics digoxin	Calcium-channel blockers diltiazem, verapamil
Antibiotics clarithromycin, erythromycin	Fibrates fenofibrate, gemfibrozil
Antifungals fluconazole, itraconazole, ketoconazole	Grapefruit juice
Antiretrovirals amprenavir, atazanavir, fosamprenavir, indinavir, ritonavir, saquinavir	Immunosuppressants cyclosporin, tacrolimus
	Statins atorvastatin, fluvastatin, pravastatin, simvastatin

Revised dosing recommendations and use in renal and hepatic impairment

Consider colchicine for acute gout when nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are contraindicated or not tolerated.¹⁵ The *Australian Medicines Handbook* recommends colchicine 1 mg followed by 0.5 mg 1 hour later for acute gout (maximum dose 1.5 mg per treatment course). No additional colchicine should be administered for at least 3 days, when a repeat course may be considered. Refer to Box 2 for information about prescribing colchicine in specific patient populations.

Because of the potential for serious toxicity, colchicine should be stopped if abdominal pain, nausea, vomiting or diarrhoea develops, irrespective of whether joint pain has been relieved.^{16,17}

A smaller colchicine pack size of 30 tablets will replace the existing 100-tablet pack later this year.¹⁹ Prescribers should consider prescribing the number of colchicine tablets sufficient for the patient's needs (see Provide patients with clear instructions about colchicine use).

Provide patients with clear instructions about colchicine use

Inform patients that colchicine can effectively relieve the pain of acute gout at doses lower than those they may have used in the past. An analgesic such as paracetamol can be taken while waiting for colchicine to take effect during an acute gout flare.¹⁵

Self-care strategies include placing an ice pack on the affected joint and using a simple device

Box 2: Colchicine prescribing considerations^{2,5,15,18}**Risk factors for colchicine toxicity**

- Renal or hepatic impairment
- Prescribing colchicine concurrently with drugs that inhibit CYP3A4 or P-gp
- Increasing age
- Gastrointestinal or cardiac disease
- High doses of colchicine

In renal or hepatic impairment

- Avoid colchicine if possible
- If no alternative therapy exists for patients with creatinine clearance < 30 mL/minute, extend the interval between colchicine treatment courses to 2 weeks during an acute gout flare
- Patients should not take strong CYP3A4 inhibitors or P-gp inhibitors at the same time as colchicine (Box 1)

To reduce the risk of serious drug interactions

In patients with normal renal or hepatic function, colchicine therapy should be stopped, or the dose reduced, when a strong CYP3A4 inhibitor or P-gp inhibitor is prescribed

such as a cardboard box to keep bedclothes off it at night.^{10,20} Advise patients to elevate the limb and avoid unnecessary clothing such as socks and shoes, when possible.²⁰

Counsel patients experiencing an acute gout flare on the revised colchicine dosing regimen:¹⁵

- take 2 colchicine tablets initially, followed by 1 colchicine tablet 1 hour later
- do not take more than 3 colchicine tablets (1.5 mg) during a course of treatment for an acute gout flare
- do not repeat the course of treatment for at least 3 days.

Discuss the safe and effective use of colchicine in acute gout. Advise patients to:^{2,15}

- tell their doctor and pharmacist about all the medicines they take, and to check before taking any new medicines
- stop taking colchicine and see their doctor if they develop nausea, vomiting or diarrhoea; unusual bleeding or bruising; muscle pain or weakness; or numbness or tingling in the fingers or toes

- avoid eating grapefruit and drinking grapefruit juice when taking colchicine
- be aware that colchicine is not a painkiller and should not be used for other causes or types of pain.

References

1. Terkeltaub RA, et al. *Arthritis Rheum* 2010;62:1060–8.
2. US Food and Drug Administration. Information for healthcare professionals: New safety information for colchicine (marketed as Colcris). 2009. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm174382.htm> (accessed 18 January 2010).
3. Ahern MJ, et al. *Aust N Z J Med* 1987;17:301–4.
4. Putterman C, et al. *Semin Arthritis Rheum* 1991;21:143–55.
5. Australian Adverse Drug Reactions Committee. Fatal interactions and reactions with colchicine: beware CYP3A4 inhibitors. *Australian Adverse Drug Reactions Bulletin* 2008;27, Number 5, Oct 2008. <http://www.tga.gov.au/adrb/aadr0810.htm>
6. Wilbur K, Makowsky M. *Pharmacotherapy* 2004;24:1784–92.
7. Kubler PA. Fatal colchicine toxicity. *Med J Aust* 2000;172:498–9.
8. Therapeutic Guidelines: Rheumatology. Version 1, 2006.
9. Zhang W, et al. *Ann Rheum Dis* 2006;65:1312–24.
10. Jordan KM, et al. *Rheumatology (Oxford)* 2007;46:1372–4.
11. Morris I, et al. *BMJ* 2003;327:1275–6.
12. Anonymous. *Prescribe Int* 2008;17:151–3.
13. Baxter K, ed. *Stockley's Drug Interactions* [online] London: Pharmaceutical Press 2009. <http://www.medicinescomplete.com> (accessed 19 March 2010).
14. Klasco RK, ed. *Drugdex System* (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA, 2010. <http://www.thomsonhc.com> (accessed 5 February 2010).
15. *Australian Medicines Handbook* 2010.
16. Aspen Pharmacare Australia. Colgout product information. 19 December 2008.
17. Aspen Pharmacare Australia. Lengout product information. 19 December 2008.
18. Medicines and Healthcare products Regulatory Agency. *Drug Safety Update* 2009;3:5.
19. Personal communication. Aspen Pharmacare Australia.
20. National Health Service Clinical Knowledge Summaries. Gout — Management. 2007. <http://www.cks.nhs.uk/gout> (accessed 18 January 2010).

PBS listing of extended-release pramipexole (Sifrol ER) for Parkinson's disease

Pramipexole extended-release (Sifrol ER) tablets have been listed on the Pharmaceutical Benefits Scheme (PBS) for treating Parkinson's disease from 1 August 2010. Unlike the immediate-release tablets, pramipexole extended-release is not PBS subsidised for restless legs syndrome.

In unpublished trials, extended-release pramipexole was more effective than placebo and had similar efficacy to that of immediate-release pramipexole in people with early (n = 539) and advanced Parkinson's disease (n = 507).^{1–3} The adverse-event profiles for the immediate- and the extended-release tablets were similar.^{1–4}

Switching

A single unpublished study investigated the efficacy and safety of an overnight switch from immediate-release to

extended-release pramipexole in people with early Parkinson's disease.^{1,5} A successful switch was defined as a less-than-15% worsening in the motor score and activities of daily living score on the Unified Parkinson's Disease Rating Scale (UPDRS) 9 weeks after switching. Most patients — 87 out of 103 patients randomised to the extended-release tablets — were successfully switched. A dose adjustment was not usually required but in some of these 87 patients the dose was increased (n = 12) or decreased (n = 3).¹

Dosing

Extended-release pramipexole is taken once daily. The tablet should not be chewed, broken or crushed. The starting dose is 375 micrograms. Titrate the dose every 5–7 days to 1500 micrograms (1.5 mg) daily. If required, increase the dose by 750 micrograms each week up to a maximum of 4500 micrograms (4.5 mg) daily.¹

Use the same daily dose if switching from the immediate-release to the extended-release product. Monitor patients after switching to ensure that their symptoms remain under control: some patients may need to have their dose adjusted.

References

1. Boehringer Ingelheim Pty Limited. Sifrol product information 16 March 2010. Australia: 2008.
2. Boehringer Ingelheim Pty Limited. A double-blind, double-dummy, placebo-controlled, randomized, three parallel groups study comparing the efficacy, safety and tolerability of pramipexole ER versus placebo and versus pramipexole IR administered orally over a 26-week maintenance phase in patients with early Parkinson's disease (PD). 2009; 8. http://trials.boehringer-ingelheim.com/res/trial/data/pdf/248.524_U09-1232.pdf (accessed 15 June 2010)
3. Boehringer Ingelheim Pty Limited. A double-blind, double-dummy, placebo-controlled, randomized, three parallel groups study comparing the efficacy, safety and tolerability of pramipexole ER versus placebo and versus pramipexole IR administered orally over a 26-week maintenance phase in L-Dopa treated patients with advanced Parkinson's disease (PD). 2009; 10. http://trials.boehringer-ingelheim.com/res/trial/data/pdf/248.525_U09-1270.pdf (accessed 15 June 2010)
4. European Medicines Agency. Assessment report for Sifrol. London: EMEA, 2009. <http://www.ema.europa.eu/humandocs/PDFs/EPAR/Sifrol/Sifrol-H-133-X-51-AR.pdf> (accessed 17 June 2010)
5. Boehringer Ingelheim Pty Limited. A double-blind, randomized, parallel groups study to assess the efficacy, safety and tolerability of switching patients with early Parkinson's disease (PD) from pramipexole IR to pramipexole ER or pramipexole IR, 2008. http://trials.boehringer-ingelheim.com/res/trial/data/pdf/248.636_U08-1964.pdf (accessed 15 June 2010)

Anakinra (Kineret) to be deleted from the PBS

On 1 December 2010, anakinra (Kineret) will be deleted from the *Schedule of Pharmaceutical Benefits*. Anakinra will continue to be available as a private prescription.

Anakinra is currently a PBS authority listing for severe active rheumatoid arthritis. It is an interleukin-1 (IL-1)

inhibitor and classified as a biological disease-modifying anti-rheumatic drug (bDMARD).

In December 2009, the Pharmaceutical Benefits Advisory Committee reviewed the clinical evidence for bDMARDs and their cost-effectiveness. The committee found that a significant price reduction was warranted for all bDMARDs listed on the PBS for rheumatoid arthritis.¹ The sponsor of anakinra did not agree to the new price, and as a result it will be removed from the PBS.²

Abatacept (Orencia), adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), and rituximab (Mabthera) remain PBS listed for severe active rheumatoid arthritis. An additional three bDMARDs will be PBS subsidised for rheumatoid arthritis from 1 August 2010: certolizumab (Cimzia), golimumab (Simponi) and tocilizumab (Actemra).²

People receiving anakinra will need to see their specialist before 1 December 2010 to consider a transition to a PBS-subsidised treatment. From May 2009 to April 2010, 225 prescriptions and repeats for anakinra were reimbursed on the PBS, enough for ongoing supply for about 20 patients.³

References

1. Australian Government Department of Health and Ageing. Public summary document: PBAC Review of bDMARDs for the treatment of severe active rheumatoid arthritis. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-bdmards-dec09> (accessed 24 June 2010).
2. Australian Government Department of Health and Ageing. Removal of anakinra (brand name Kineret) from the Pharmaceutical Benefits Scheme (PBS) for the treatment of severe active rheumatoid arthritis. http://www.pbs.gov.au/html/healthpro/news/article?id=NEWS-2010-6-30-Removal_of_Kineret.xml (accessed 5 July 2010).
3. Medicare Australia. PBS item statistics. https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml (accessed 24 June 2010).

Exenatide (Byetta): first in another new class of diabetes drugs

Exenatide is an injectable drug in the new class of incretin mimetics, PBS listed from 1 August 2010 for type 2 diabetes. The listing is for combination therapy as either:

- dual therapy, with metformin or a sulfonylurea, where HbA_{1c} exceeds 7% and the patient cannot take these drugs together, or
- triple therapy, with metformin and a sulfonylurea, where HbA_{1c} exceeds 7% despite maximally tolerated doses of both drugs.

An in-depth RADAR review of exenatide will be published online before our December print issue. To receive the exenatide review as soon as it is available, subscribe to the RADAR email alert at www.nps.org.au/radar.