

In Brief

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

Varenicline (Champix) safety update: serious neuropsychiatric and dermatological adverse events

Serious neuropsychiatric symptoms and severe skin reactions have been reported in people taking varenicline. Updated advice on managing neuropsychiatric symptoms and a precaution about rare but potentially fatal skin reactions have been added to the product information.¹

Since its launch, drug regulatory agencies in Australia and overseas have raised concerns about possible psychiatric events with varenicline.^{2–5}

Discuss with patients the potential risks and benefits of varenicline for smoking cessation. Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [then click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

For more information about varenicline for smoking cessation read the January 2008 full *NPS RADAR* review *Varenicline (Champix) for smoking cessation*.

Monitor all patients for changes in behaviour or thinking, anxiety, psychosis and mood swings

Cases of suicidality (suicidal thinking and suicidal behaviour) in people taking varenicline were identified in a postmarketing safety review by the US Food and Drug Administration (FDA).⁶ The FDA review identified 116 reports of suicidal thinking and 37 reports of suicidal behaviour (half of which [19] resulted in death) in people who started varenicline between May 2006 and November 2007. Of 128 cases that reported time-to-onset of suicidal events, most (86%) occurred during treatment with varenicline. About half the reported suicidal events occurred in people with a history of psychiatric illness.⁶

Advise people taking varenicline and their families of the need to stop varenicline immediately and seek urgent medical advice if they experience symptoms including:

- changes in behaviour or thinking
- anxiety
- psychosis
- mood swings
- suicidal thoughts or behaviours.

Ongoing follow-up of patients with neuropsychiatric symptoms is recommended until symptoms resolve.¹

Postmarketing reports of rare but potentially fatal skin reactions

Rare but severe and potentially fatal cutaneous reactions, including Stevens–Johnson syndrome and erythema multiforme, have been reported in people taking varenicline. The updated Australian product information advises patients to stop taking varenicline and contact their health professional at the first sign of a rash or skin reaction.

For information about reporting adverse reactions, see the TGA website.

References

- 1 Pfizer Australia Pty Ltd. Champix product information. 29 July 2009.
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- 3 Health Canada. Canadian Adverse Reaction Newsletter 2008;18:1–2. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v18n2-eng.pdf
- 4 Medicines and Healthcare products Regulatory Agency and Commission on Human Medicines. Drug Safety Update 2008;2. <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON030923>
- 5 US Food and Drug Administration. Public Health Advisory: FDA Requires New Boxed Warnings for the Smoking Cessation Drugs Chantix and Zyban. 2009. <http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm169988.htm> (accessed 2 November 2009).
- 6 US Food and Drug Administration. FDA Drug Safety Newsletter 2009;2. <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm107311.htm>

Etoricoxib (Arcoxia): be aware of hypertension risk

Etoricoxib (Arcoxia) is a new COX-2 selective NSAID that became available in Australia on private prescription in August 2009. It is not listed on the PBS. In July 2008 the Pharmaceutical Benefits Advisory Committee (PBAC) rejected an application to list etoricoxib on the PBS for osteoarthritis, concluding that there was no demonstrated need to list another COX-2 selective NSAID and that etoricoxib appears to cause more episodes of hypertension than celecoxib.¹

In most other respects the efficacy and safety of etoricoxib are similar to those of celecoxib. In 2 trials comparing celecoxib 200 mg once daily with etoricoxib 30 mg once daily in people with osteoarthritis, over 26 weeks etoricoxib was no worse than celecoxib at reducing pain and improving function.² The 2 drugs are likely to have similar gastrointestinal safety, although only imprecise estimates of the comparative rates of serious gastrointestinal injury (e.g. perforations, obstructions and bleeding) are available.³

For more information about the efficacy and safety of etoricoxib, refer to the *Australian Prescriber* October 2009 News Drugs article.

Etoricoxib is contraindicated for people with uncontrolled hypertension

Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. It is contraindicated for patients with existing hypertension whose blood pressure is persistently above 140/90 mm Hg.⁴

Over 26 weeks of treatment in trials the incidence of any recorded hypertension-related adverse event was higher with etoricoxib 30 mg than with celecoxib 200 mg (5.7% vs 2.3%, 95% CI of difference 0.97–6.10).⁵ Compared with diclofenac, etoricoxib was also associated with a significantly higher risk of hypertension, oedema and heart failure (pooled data for etoricoxib 60 mg and 90 mg doses).⁵

Dosing issues

For symptomatic treatment of osteoarthritis, the recommended dose is etoricoxib 30 mg once daily, increased to 60 mg once daily for patients with insufficient relief from symptoms. Etoricoxib 120 mg once daily is approved for a maximum 8 days for acute flares of gouty arthritis, and for acute analgesia including dental pain and primary dysmenorrhoea.⁴

Assess the risk of new or continuing NSAID use

When assessing the need for NSAID therapy, weigh the risk of cardiovascular, renal and gastrointestinal effects against the potential benefits of treatment for each patient. Elevated cardiovascular risk has been associated with COX-2 selective NSAIDs in some studies. A pooled analysis comparing etoricoxib 30 mg daily or higher with naproxen 1000 mg daily found a significantly higher rate of serious thrombotic cardiovascular events with etoricoxib.⁴ Evidence for the long-term cardiovascular safety of conventional NSAIDs is limited and does not provide strong evidence of a lower risk than for COX-2 selective NSAIDs.

Using a COX-2 selective NSAID is most justified in people at higher risk of gastrointestinal adverse effects (see *NPS RADAR* August 2005: *Elevated cardiovascular risk with NSAIDs?*). In the general NSAID-using population, the incidence of serious ulcer complications is low, so the absolute reduction in the risk of complications when using a COX-2 selective NSAID rather than a conventional NSAID is small for most people. An alternative gastroprotective strategy for people at high risk is to co-prescribe a conventional NSAID with a proton-pump inhibitor, double-dose H₂ antagonist, or misoprostol (see *NPS News 46: Proton pump inhibitors*).

References

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2. Bingham CO, 3rd, et al. *Rheumatology (Oxford)* 2007;46:496–507.
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4. Merck Sharp & Dohme (Australia) Pty. Limited. Arcoxia product information. 17 July 2009.
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New pneumococcal polysaccharide conjugate vaccine (Synflorix) added to the national immunisation schedule

Synflorix is a 10-valent pneumococcal polysaccharide conjugate vaccine for *Streptococcus pneumoniae*.^{*1} The Pharmaceutical Benefits Advisory Committee recommended listing the vaccine on the National Immunisation Program as a 4-dose schedule (2, 4, and 6 months and a booster between 1 and 2 years), concluding that it is equivalent to the standard 3-dose schedule of 7-valent pneumococcal conjugate vaccine (Prevenar). Either vaccine is recommended for immunising Australian infants and children from the age of 8 weeks to 2 years against pneumococcal disease (e.g. invasive disease, pneumonia and acute otitis media).^{2,3}

New information about prophylactic paracetamol use

Routine use of paracetamol at the time of vaccination is no longer recommended.³ However, a prophylactic antipyretic is recommended when administering pneumococcal vaccines to children with seizure disorders or with a prior history of febrile seizures.^{4,5}

Paracetamol can be given after vaccination if an infant or child has a fever of $> 38.5^{\circ}\text{C}$. The dose is 15 mg/kg paracetamol liquid, up to a maximum daily dose of 90 mg/kg/day in 4–6 divided doses for up to 48 hours.³

Clinical trial data suggest that using prophylactic paracetamol might reduce the immune response to conjugate pneumococcal vaccines and some other paediatric vaccines, although it is unknown if the reduction is clinically relevant.^{1,6,7} An effect on antibody concentrations has been seen with both the 10-valent vaccine (Synflorix) and the 7-valent vaccine (Prevenar).^{6,7} Other antipyretics, such as ibuprofen, may have a similar effect, but there are no data.

Infants who received prophylactic paracetamol in 1 trial had lower antibody concentrations after the primary vaccination with the 10-valent vaccine than infants who did not receive paracetamol. The difference in antibody concentrations was larger for some serotypes than for others.^{6,7}

* The 10-valent vaccine includes polysaccharide serotypes 1, 5 and 7F in addition to those in the 7-valent pneumococcal conjugate vaccine (Prevenar).

The significance of the lower post-primary antibody response is unclear, but the data from 12–15 months after the booster dose suggest that any impact on efficacy should be limited. After receiving booster doses, similar proportions of children achieved target levels of anti-pneumococcal antibodies, regardless of whether they received paracetamol (with the exception of 1 measure of response to serotype 6B).^{6,7}

References

1. GlaxoSmithKline Australia Pty Ltd. Synflorix product information. 2 July 2009.
2. Australian Government Department of Health and Ageing. July 2009 PBAC outcomes: positive recommendations. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacrec-jul09-positive> (accessed 7 October 2009).
3. Australian Technical Advisory Group on Immunisation. The Australian Immunisation Handbook, 9th edn. 2008. <http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook-home> (accessed 7 October 2009).
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Montelukast (Singulair) PBS listed for exercise-induced asthma in children aged 6–14 years

The Pharmaceutical Benefits Scheme (PBS) listing for montelukast 5 mg tablets was extended on 1 December 2009 to include preventing exercise-induced asthma in children aged 6–14 years. This Streamlined Authority listing is intended for children whose asthma is otherwise well controlled with an inhaled corticosteroid (ICS), but who require a short-acting beta₂ agonist 3 or more times per week for residual exercise-related symptoms. For these children, adding montelukast to continuing ICS treatment is an alternative to adding a long-acting beta₂ agonist (LABA; i.e. eformoterol or salmeterol).

Montelukast is not intended to be used in combination with a LABA under this listing. This means it cannot be prescribed for children already using a fixed-dose combination inhaler containing budesonide with eformoterol (Symbicort) or fluticasone with salmeterol (Seretide). The listing therefore does not cover using montelukast in addition to budesonide with eformoterol in a maintenance and reliever regimen (SMART).

Assess the nature and severity of exercise-induced symptoms

Note that exercise-induced symptoms often indicate that the patient's asthma is not well controlled. Rule out poor adherence and poor inhaler technique before stepping up drug therapy.

Ensure that children correctly distinguish exercise-induced asthma from being short of breath during exercise. Symptoms of exercise-induced asthma get worse for 5–10 minutes after the exercise stops, then recover over the next 30 minutes or so.¹

Non-drug strategies may be useful and physical fitness can raise the threshold of exercise intensity that provokes exercise-induced asthma.¹

Dosing issues

There are different PBS listings of montelukast for younger and older children (Table 1). Montelukast is also available as a 10 mg film-coated tablet, indicated for adolescents over 15 years and adults, but is not PBS listed for this age group. Children with asthma should take montelukast once daily in the evenings.²

Table 1. PBS listings of montelukast

Age of child	Indications	
	Frequent intermittent or mild persistent asthma* (when not requiring an ICS)	Exercise-induced asthma persisting after optimal dose of ICS†
2–5 years	4 mg chewable tablet	<i>Not listed</i>
6–14 years	5 mg chewable tablet	5 mg chewable tablet

* First-line preventer, as the single preventer agent, as an alternative to sodium cromoglycate or nedocromil sodium. Not for use in combination with a LABA

† As an alternative to a LABA

References

1. National Asthma Council Australia. Asthma Management Handbook. 2006. <http://www.nationalasthma.org.au/cms/index.php> (accessed 11 November 2009).
2. Merck Sharp & Dohme (Australia) Pty. Limited. Singulair product information. 16 June 2009.

Authority listing for ciprofloxacin ear drops (Ciloxan) extended

The authority listing for ciprofloxacin ear drops (Ciloxan) was extended on 1 November 2009 to allow prescribing for children with chronic suppurative otitis media (CSOM) with perforation of the tympanic membrane or a grommet.¹ The authority listing of ciprofloxacin ear drops was previously restricted to CSOM in Aboriginal and Torres Strait Islander people.²

CSOM is a common cause of preventable hearing impairment. Because CSOM usually occurs in the first 5 years of life — when most speech and language development occurs — it may contribute to delayed speech, language and learning³, with negative consequences for socialisation, education and employment.

Ciprofloxacin is not first-line because of the risk of resistance but may be useful when > 7 days of therapy is needed, or there is a perforated tympanic membrane or a grommet.^{4,5} For short-term use (< 7 days), ear drops containing an aminoglycoside (e.g. framycetin) are recommended and appear to be safe.⁴ However, in the presence of a perforated tympanic membrane or grommet use of ear drops containing an aminoglycoside is controversial because of the risk of ototoxicity.^{4,5} Before instilling ear drops, perform aural toilet to remove debris and discharge — that is, 6-hourly, meticulous, gentle dry mopping with rolled tissue spears until the ear canal is dry.^{4,5}

References

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