

## 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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

### Fosphenytoin

Pro-Epanutin (Pfizer)

10 mL vials containing 75 mg/mL

Approved indication: epilepsy

Australian Medicines Handbook Section 16.1.3

Phenytoin sometimes has to be given parenterally, for example to stop status epilepticus. Intramuscular injections are not recommended because of local adverse reactions and unpredictable absorption. The injection is not very soluble and can be precipitated if given with other intravenous infusions. Injectable phenytoin is pH 12 so the intravenous line must be flushed with saline to reduce local venous irritation. Fosphenytoin has been developed to try and reduce these practical problems.

Fosphenytoin is a prodrug. It is converted rapidly (half-life 15 minutes) to phenytoin. Fosphenytoin is less alkaline than phenytoin and can be given by intramuscular injection. This route is not recommended in status epilepticus as peak plasma concentrations are not reached for 30 minutes.

The pharmacokinetics are complex. Fosphenytoin is highly bound to plasma proteins. It displaces phenytoin from binding sites, increasing the unbound fraction of phenytoin. To reduce confusion about the dose of fosphenytoin it is expressed as phenytoin equivalents. (A fosphenytoin concentration of 75 mg/mL is equivalent to 50 mg/mL of phenytoin sodium.)

When the prodrug is converted to phenytoin, formaldehyde and phosphate are also produced. These compounds are not thought to cause adverse reactions, but the phosphate load needs to be considered in patients with renal impairment. Renal and hepatic dysfunction can also result in changes to protein binding. Many drugs can alter phenytoin concentrations, but none are known to affect the conversion of fosphenytoin.

Adverse reactions include hypotension and central nervous system depression. Some patients will complain of itching or paraesthesia. The safety (and effectiveness) of fosphenytoin has not been assessed for longer than five days.

In Australia fosphenytoin has been approved for use in generalised convulsive status epilepticus and the prevention and treatment of seizures occurring in connection with neurosurgery and/or head trauma.

### Rivastigmine

Exelon (Novartis)

1.5 mg, 3 mg, 4.5 mg and 6 mg capsules

Approved indication: Alzheimer's disease

Australian Medicines Handbook Section 16.5.1

Acetylcholinesterase inhibitors have been studied in Alzheimer's disease as they enhance the remaining cholinergic

neurotransmission. Rivastigmine is the third inhibitor to be marketed. Tacrine and donepezil are already available.

Rivastigmine inhibits acetyl- and butyrylcholinesterase resulting in increased acetylcholine at cholinergic synapses. It is rapidly metabolised by cholinesterases and has a plasma half-life of one hour. Most of a dose is excreted by the kidneys with no unchanged drug appearing in the urine. The pharmacokinetics are non-linear; the bioavailability triples when the dose is doubled.

A multicentre trial studied 725 patients with mild to moderate Alzheimer's disease. These patients were randomised to receive rivastigmine 1–4 mg/day or 6–12 mg/day or a placebo. The dose of rivastigmine was titrated in the first 12 weeks of the 26-week trial. There were 'meaningful' improvements of cognitive function in 24% of the 242 patients given the higher dose of rivastigmine and in 16% of the 238 patients given a placebo.<sup>1</sup> The outcome for the lower dose was not significantly different from placebo.

Over 30% of the patients randomised to take the higher dose of rivastigmine discontinued, with approximately 23% withdrawing because of adverse events.<sup>1</sup> Common adverse effects are nausea, vomiting, anorexia and dizziness. These adverse effects often occur while the dose is being titrated.

Although rivastigmine had advantages over placebo in the rating scales used in the trial<sup>1</sup>, their clinical relevance is uncertain. Significantly more patients taking higher doses of rivastigmine had an improvement of at least 10% on the progressive deterioration scale, however this difference is relatively small. In the placebo group 19% of the patients improved compared with 29% of those taking rivastigmine. As the clinical response cannot be predicted in the patients who can tolerate rivastigmine, treatment should stop if there is no benefit after 12 weeks. Alzheimer's disease is chronic and progressive so studies lasting longer than six months are needed.

#### REFERENCE

1. B303 Exelon Study Group. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *Br Med J* 1999;318:633-8.

#### NEW FORMULATIONS

##### Diltiazem hydrochloride

Cardizem (Aventis Pharma)

60 mg tablets

##### Gabapentin

Neurontin (Pfizer)

800 mg tablets

**Olanzapine**

Zyprexa Zydis (Eli Lilly)  
5 mg and 10 mg wafers

**Ursodeoxycholic acid**

Ursofalk (Orphan)  
250 mg/5 mL suspension

**NEW COMBINATIONS**

**Oestradiol/norethisterone acetate**

Estalis 50/140 (Novartis)  
Patches delivering 50 microgram oestradiol and 140 microgram norethisterone acetate daily  
Estalis 50/250 (Novartis)  
Patches delivering 50 microgram oestradiol and 250 microgram norethisterone acetate daily  
Estalis Sequi 50/140 (Novartis)  
Patches delivering 50 microgram oestradiol daily for weeks one and two, and 50 microgram oestradiol and 140 microgram norethisterone acetate daily for weeks three and four  
Estalis Sequi 50/250 (Novartis)  
Patches delivering 50 microgram oestradiol daily for weeks one and two, and 50 microgram oestradiol and 250 microgram norethisterone acetate daily for weeks three and four

**Perindopril/indapamide**

Coversyl Plus (Servier)  
perindopril 4 mg/indapamide 1.25 mg tablets

**NEW PROPRIETARY BRANDS**

**Hepatitis A vaccine, inactivated**

Avaxim (Aventis Pasteur)  
0.5 mL pre-filled syringes

**Insulin aspart**

NovoRapid (Novo Nordisk)  
3 mL penfill cartridges for use in NovoPen 3, NovoPen 3 Demi and Innovo  
NovoLet (Novo Nordisk)  
3 mL pre-filled syringes

**Answers to self-test questions**

1. False	3. False	5. True
2. False	4. True	6. True
7. False	9. False	
8. True	10. False	

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