News from Pharma 2004-05
Extracted from Palliativedrugs.com newsletters

Discontinued products

June/July 2004
i) Nefopam hydrochloride injection 20mg/ml (Acupan®) has been discontinued. There is no alternative UK supplier.

August 2004
i) Ensure® powder 380g and Enrich® chocolate-flavoured liquid 250ml have been discontinued. A list of the products, flavours and pack sizes in the range is available from Abbott Laboratories (01628 773355).

September 2004
i) Concord Pharmaceuticals (0845 602 0137) has discontinued phenobarbital 200mg/ml injection (Gardenal®). Alternative supplies can be obtained from Martindale Pharmaceuticals (01277 266600).

ii) Pfizer (01304 616161) is discontinuing the Farlutal® brand of medroxyprogesterone acetate 100, 250 and 500mg tablets from October 1st 2004. The injection will remain available.

The company is recommending its Provera® brand as an oral alternative. However, because studies have shown that Provera® has higher bio-availablity than Farlutal®, the dosage instructions for Provera® should be followed.

October 2004
i) Forest Laboratories (01322 550550) has discontinued Fletcher's Enemette (docusate sodium 90mg and glycerol 3.78g/5ml) because of a manufacturing problem. Other enema products made by Forest Laboratories are not affected and remain available.

November/December 2004
i) Bristol-Myers Squibb (020 8572 7422) has discontinued nalbuphine (Nubain®) injection because of ongoing manufacturing problems and low demand.

January/February 2005
i) Following the recent CSM safety review, the MHRA is withdrawing co-proxamol in the UK. It will be phased out over the next 6—12 months to allow patients time to switch to suitable alternatives.

ii) Janssen (01494 567567) has voluntarily cancelled its UK marketing authorisations for cisapride (Prepulsid®) and so will no longer be able to manufacture it in the UK or import it. The tablets will remain available under existing named-patient arrangements for as long as UK stocks last. However, their expiry date is the end of June 2005. Stocks of the oral suspension are already exhausted. Importing companies are unable to supply cisapride to the UK because of CSM/MHRA safety restrictions.

March 2005
i) Novartis (01276 692255) is voluntarily withdrawing thioridazine (Melleril®) worldwide by June 30th. Other UK generic formulations are also being withdrawn.

In a letter to health professionals, Novartis explains that this is because thioridazine-induced QTc prolongation has been associated with cardiac arrhythmias and sudden death in schizophrenic patients. The availability of newer antipsychotics with a superior benefit/risk profile now mean that thioridazine does not meet clinical and regulatory expectations.

The company advises that no new patients should be started on thioridazine and that existing patients should have the drug withdrawn gradually to minimise the risk of symptom recurrence or cholinergic rebound. This could be achieved by cross-tapering doses with the chosen alternative antipsychotic.

April/May 2005
i) Relevant product discontinuations in BNF 49 (March 2005) that have not been mentioned in palliativedrugs.com newsletters:

- carbenoxolone sodium gel (Bioral®). For alternative cytoprotectants for oral inflammation, see PCF2 pp. 274–276
- azapropazone capsules 300mg and 600mg (Rheumox®). There is no alternative UK supplier

New products

August 2004
i) Pregabalin (Lyrica®), a GABA analogue, has been approved in the EU for the treatment of peripheral neuropathic pain and as an adjunctive therapy for partial epilepsy. It has so far been studied in diabetic neuropathy and post-herpetic neuralgia, but not in cancer-related neuropathic pain.

Pregabalin has been released on a limited basis to hospitals in the UK. General release is expected in September. The starting dose in neuropathic pain is 150mg o.d. This can be increased to 300mg o.d. after 3 to 7 days, then to 600mg after a further 7 days if needed.

ii) DepoDur™, a sustained release epidural injection of morphine, has been approved by the FDA for the treatment of pain following major surgery. A single dose is claimed to provide pain relief for up to 48 hours. A USA launch is expected at the end of 2004 and a licensing application has also been submitted to the MHRA in the UK.

October 2004
i) Pfizer have released pregabalin, a GABA analogue, for use in the community. For details on the use of pregabalin in neuropathic pain, see the August 2004 newsletter.

Lyrica®
Capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 300mg, 28 days @ 300mg o.d. = £32.20.

ii) Duloxetine, a combined serotonin and noradrenaline re-uptake inhibitor, has been approved in the USA for the treatment for peripheral neuropathic pain in diabetes. A licence application has also been submitted in the UK and approval is expected in early 2005.

The US approval was based on the results of two 12-week studies in patients with peripheral neuropathy and moderate or moderately severe pain present for an average of 4 years. Compared with placebo, duloxetine reduced average pain levels over 24h and relieved night-time pain.

Duloxetine is co-marketed by Lilly (01256 315999) and Boehringer Ingelheim (01344 424600) under the brand names Cymbalta™ in the USA (where it is also approved as an antidepressant) and Yentreve™ in the UK (where it is approved for stress incontinence in women).

January/February 2005
i) Standard mirtazapine tablets 30mg (i.e. *not* orodispersible) are now available from PLIVA (01730 710900). The company plans to introduce further strengths in the future.

Mirtazapine (non-proprietary)
Tablets 30mg, 28 days @ 30mg o.n. = £20.49.

March 2005

i) From January 31st 2005, Janssen-Cilag (01494 567567) will be gradually replacing reservoir-type fentanyl transdermal patches with the new matrix patches (Durogesic DTrans®. Prices remain the same for the four strengths available.

ii) Risperidone is now available as orodispersible tablets 0.5mg (Risperdal Quicklets®).

iii) UCB Pharma (01923 211811) has introduced methylphenidate modified release capsules 10, 20 and 30mg (Equasym XL®). These contain 30% immediate release and 70% extended release methylphenidate.

Cost of 28 days treatment @ 10mg, 20mg or 30mg o.d. = £23.33, £28 and £32.67, respectively.

Changes to existing UK products

June/July 2004
i) Oxycodone capsules, injection and tablets m/r (OxyNorm®/OxyContin®) are now licensed for use in severe non-cancer pain. Full details can be found in the relevant SPCs.

ii) Ipratropium bromide metered dose inhaler 20microgram/dose is now CFC-free.

August 2004
i) CP Pharmaceuticals (01978 661261) is re-instating the 'break seal' on diamorphine ampoule packs and these should be available in a couple of months.

ii) The SPCs for olanzapine (Zyprexa®) and risperidone (Risperdal®) now state that they should not be used to treat dementia-related psychosis and/or behavioural disturbances in elderly patients. This follows recent CSM safety alerts advising that there is a 3-fold increase in the risk of cerebrovascular adverse events (CVAEs) compared with placebo (see the May 2004 newsletter).

The SPC for risperidone further states that treatment of acute psychosis in patients with a history of dementia should be limited to the short term and be undertaken only under specialist advice. Physicians should also consider the risk of a CVAE before treating patients with a history of stroke or transient ischaemic attack, or with risk factors for cerebrovascular disease such as hypertension, diabetes, smoking, etc.

iii) Macrogol 3350 (Movicol®) is now licensed for extended use in severe chronic or resistant constipation, including that caused by regular use of opioids or antimuscarinics. The recommended dose is one or two sachets daily.

iv) The SPC for sodium valproate (Epilim®, Epilim IV® and Epilim Chrono®) has been updated to include precautions relating to patients with hepatic insufficiency concurrently receiving sodium valproate and salicylates (e.g. aspirin). Aspirin inhibits the metabolism of sodium valproate and also displaces it from its protein binding sites. This may increase sodium valproate levels and cause undesirable effects. The company state that this warning does not apply to other NSAIDs.

September 2004
i) MSD has suspended the production of dexamethasone 0.5mg tablets (Decadron®) because of manufacturing difficulties. Based on current demand, existing stocks should last until late September 2004.

The company is ensuring that alternative supplies will be available. Further details can be obtained from MSD (01992 467272).

October 2004
i) The SPC for domperidone (Motilium®) now includes data on an interaction with ketoconazole resulting in a slight increase in the QT interval (<10msec).

This was observed during a pharmacokinetic study in which plasma domperidone levels and the area under the plasma concentration-time curve were increased approximately 3-fold when ketoconazole was co-administered orally. This occurred because ketoconazole inhibits CYP 3A4, the cytochrome P450 enzyme responsible for the metabolism of domperidone.

The SPC now advises caution if other strong CYP3A4 inhibitors (e.g. erythromycin) are co-prescribed with domperidone and recommends considering an alternative to ketoconazole if antifungal treatment is required.

January/February 2005

i) Ivax Pharmaceuticals (0800 451600) has recalled all batches of lorazepam 1mg and 2.5mg tablets supplied since June 2002 because stability tests indicate they may lose effectiveness before the end of their shelf life. There is no expected patient risk and this action is precautionary.

ii) Darbepoetin injection 500microgram/ml (Aranesp®) is now licensed for administration once every 3 weeks for treating anaemia (defined as a haemoglobin level <11g/dl) in adult patients with non-myeloid cancers undergoing chemotherapy. The recommended starting dose is 6.75microgram/kg SC every 3 weeks. If symptoms (e.g. fatigue) have not responded or the haemoglobin level has not reached 12g/dl after 9 weeks, further treatment may be ineffective. See the SPC for full details and alternative regimens.

iii) Further to our item in the November/December 2004 newsletter, Novartis (01276 692255) has added a caution regarding osteonecrosis of the jaw to the zoledronic acid (Zometa®) SPC. The company recommends that patients should avoid invasive dental procedures if possible during treatment, and undergo a dental examination with appropriate preventive work before starting treatment.

March 2005

i) The SPC for ondansetron (Zofran®) now contains warnings that the potent cytochrome P450 3A4 inducers phenytoin, carbamazepine and rifampicin can increase the clearance of ondansetron. Further, small studies have indicated that ondansetron may reduce the analgesic effect of tramadol.

ii) Venous thromboembolism (VTE) is now listed as a very rare (<0.01%) undesirable effect of olanzapine injection (Zyprexia®). Although no causal relationship has been established, the company advises that preventive measures against any risk factors for VTE should be undertaken during treatment.

iii) Macrogol 3350 and electrolytes (Movical Paediatric Plain®) is now licensed for the treatment of chronic constipation and prevention of recurrent faecal impaction in children. The usual starting dose is 1 sachet o.d. for children aged 2—6 years and 2 sachets o.d. for those aged 7—11 years.

iv) The SPC for disodium pamidronate (Aredia®) has been updated with a warning regarding very rare (<0.01%) cases of osteonecrosis of the jaw. Please see our November/December 2004 newsletter for details.

Palliative care prescribing changes in BNF 48, September 2004

i) Updated advice on management of chronic obstructive pulmonary disease and asthma

Sections 3.1 and 3.2 contain advice on managing COPD and asthma, which has been updated to reflect the clearer roles of bronchodilators and corticosteroids. The advice is based on recent COPD guidelines issued by the National Institute for Clinical Excellence (NICE) and asthma guidelines issued by the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (SIGN).

Section 3.7 is now more positive about the benefits of mucolytics in reducing exacerbations in patients with COPD and productive cough.

ii) Committee on Safety of Medicines (CSM) advice on atypical antipsychotics and risk of stroke

Section 4.2.1. now contains CSM advice on reducing the risk of stroke in elderly patients taking olanzapine and risperidone.

This advice was outlined in our May 2004 newsletter.

iii) New guidelines on antibacterial treatment of cellulitis

Section 5.1 (Table 1) now recommends using benzylpenicillin *or* phenoxymethylpenicillin *plus* flucloxacillin for treating cellulitis. Flucloxacillin should be discontinued if streptococcal infection is confirmed.

Erythromycin is advised for penicillin-allergic patients.

iv) Wider dose range for naloxone in opioid overdose

The recommended dose range for naloxone in opioid overdose has been widened from 800micrograms—2mg to 400micrograms—2mg, repeated at 2—3min intervals to a maximum of 10mg if respiratory function does not improve.

v) Higher dose of ranitidine for prophylaxis of NSAID-induced gastric or duodenal ulcer.

The recommended dose of ranitidine for prophylaxis of NSAID-induced gastric or duodenal ulcer is now 300mg b.d., not 150mg b.d.

Palliative care changes in BNF 49, March 2005

a) Guidance on prescribing in palliative care
Pregabalin (Lyrica®) is now listed as a treatment for neuropathic pain.

b) Section 1.6.4 now states that Macrogol 3350 with electrolytes (Movicol-Half®) is *not* recommended for faecal impaction in children; use Movicol Paediatric Plain® instead (see the March 2005 newsletter for details).

c) Section 2.8.1 contains new dosing information for dalteparin (Fragmin®). The dose for prophylaxis of deep vein thrombosis in medical patients is 5000units o.d. SC.

d) Section 4.3 (Antidepressant drugs)
i) Section 4.3.3 now gives maximum recommended doses for paroxetine (Seroxat®). Doses of >20mg/day are not considered necessary for depression.
ii) New CSM cautions on the cardiovascular safety of venlafaxine (Efexor®) have been added to section 4.3.4 (see the March 2005 newsletter for details).

e) Section 4.7.1 notes the impending discontinuation of co-proxamol (see the January/February 2005 newsletter for details) and recommends that no new patients should be started on it.

f) Chapter 5 (Infections) has been extensively updated.
iii) Section 5.2 now states that the PO dose for fluconazole for preventing relapse of cryptococcal meningitis in AIDS patients is 200mg o.d. (the IV dose remains at 100–200mg/day).
v) Doses for the combined clindamycin/primaquine regimen for *Pneumocystis* pneumonia in section 5.4.8 have been changed. They are now clindamycin 600mg q8h (instead of q6h) PO and primaquine 30mg o.d. (instead of 15mg o.d.) PO. The combination is still *unlicensed* and is associated with considerable toxicity.
g) Section 9.1.3 includes an alternative initial dosing regimen for darbepoetin alfa (Aranesp®) in patients with non-myeloid cancers receiving chemotherapy (see the January/February 2005 newsletter for details).