Summary of New and Discontinued Products and Changes to UK Products 2004

January 2004

(i) Morphine sulphate (Sevredol®) oral solution 10mg/5ml and 20mg/ml

Both strengths of morphine sulphate (Sevredol®) oral solution have been discontinued by Napp Pharmaceuticals (01223 424444). This was an alcohol-free preparation, suitable for use as a mouth wash for mucositis. Alcohol and alcohol-free alternative preparations are:

Morphine sulphate (Martindale 01277 266600)
Oral solution 10mg/5ml (*contains ~8% alcohol*).

Oramorph® (Boehringer Ingelheim 01344 424600)
Oral solution 10mg/5ml (*contains ~10% alcohol*).
Oral solution unit dose vials 10mg, 30mg, 100mg/5ml (*all alcohol free*).
Concentrated oral solution 100mg/5ml (*alcohol free*).

(ii) Piroxicam 20mg suppositories

Piroxicam 20mg suppositories (Feldene®) have been discontinued by Pfizer (01304 616161). There are no alternative manufacturers.

(iii) Metoclopramide 5mg tablets

Metoclopramide 5mg tablets (Maxolon®) have been discontinued by Shire pharmaceuticals (01256 894000). The 10mg tablets and all other products in this range remain.

February 2004

i) Buccal midazolam

The injectable formulation of midazolam 5mg/ml is being used via the unlicensed buccal route for the treatment of tonic-clonic seizures, generally as an alternative to rectal diazepam. A more concentrated solution (10mg/ml) for buccal administration, is now available in the UK as a special order.

Hypnovel (Roche 0800 328 1629)
Injection midazolam 5mg/ml, 2ml amp = £0.81.

Epistat
Buccal oral solution midazolam 10mg/ml, 5ml bottle = £15.00. (Unlicensed, available as a special order from Special Products 01932 820666; see Special orders and named patient supplies.

March 2004

(i) Olanzapine injection

Olanzapine powder for solution for injection (Zyprexa, Eli Lilly 01256 315000) has been launched. It is licensed for the rapid control of agitation and disturbed behaviours at a dose of 5-10mg IM. Each 10mg vial costs £3.48. Intravenous and subcutaneous use was not investigated for the licensing application. If anyone has any information or experience of using this product by the subcutaneous route please e-mail us at hq@palliativedrugs.com.

(ii) Orodispersible mirtazapine

Following our report in the November/December 2003 newsletter surrounding the launch of an orodispersible mirtazapine 30mg tablet (Zispin SolTab), Organon has now launched 15mg and 45mg orodispersible tablets. The tablets dissolve on the tongue without water. The tablets will also fully disperse in water, however the company has no information on suitability for administration via feeding tubes.

Mirtazapine (non-proprietary)
Oral solution 15mg/ml, 28 days @30mg o.n = £39.88.

Zispin (Organon 01223 432700)
Tablets 30mg, 28 days @30mg o.n = £22.92.
Tablets orodispersible 15mg, 30mg, 45mg, 28 days @30mg o.n = £19.25.

(iii) Zoledronic acid infusion

From the 8th March 2004, zoledronic acid (Zometa, Novartis 01276 692255) infusion will be supplied as 4mg/5ml concentrate solution instead of a powder and solvent. The concentrate must still be further diluted with 100ml saline or 5% glucose soution and given over 15 minutes. The cost is unchanged (see zoledronic acid monograph).

(iv) Discontinuation of venlafaxine 50mg tablets

Venlafaxine 50mg tablets (Efexor, Wyeth 01628 415330) are being discontinued and stocks are likely to be exhausted by July. The other strengths of venlafaxine tablets and modified release capsules will remain (see venlafaxine monograph).

April 2004

a) Palliative care prescribing changes in March 2004 BNF 47

i) Selective serotonin re-uptake inhibitors (SSRIs) not to be used in those under 18 years of age

The Committee on the Safety of Medicines (CSM) has advised that the SSRIs citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as well as venlafaxine should *not* be used in those under 18 years of age to treat depressive

illness. Trials suggest an increase in the risk of harmful outcomes including self-harm and suicide.

ii) Dose tapering of dexamethasone for cerebral oedema

The treatment of cerebral oedema with dexamethasone has been changed. Previously the guidance was;
'Dexamethasone (as *phosphate*) 10mg IV, then 4mg IM every 6hours as required for 2-10 days'

This has been changed to;
'Dexamethasone (as *phosphate*) 10mg IV, then 4mg IM every 6hours as required for 2-4 days, then gradually reduced and stopped over 5-7 days'.

iii) Maximum dose of rectal diazepam

A maximum dose of rectal diazepam has been introduced. No more than 30mg (15mg in the elderly) should be administered via the rectum for convulsions. This can be repeated after 12hours.

b) New and discontinued products and changes to UK products

i) Mirtazepine supply

Following the launch of mirtazepine orodispersible tablets (Zispin® SolTab), as announced in last month's newsletter, the original mirtazepine tablets (Zispin®) are being discontinued on 4th May. The new orodispersible tablets (15mg, 30mg and 45mg) are bioequivalent to the plain tablets. For further details contact medical information at Organon (01223 432700).

ii) Ibandronic acid tablets and injection

Ibandronic acid 50mg tablets (Bondronat®, Roche) have been launched. They are indicated for the prevention of skeletal events in patients with breast cancer and bone metastases at a dose of 50mg daily. Ibandronic acid concentrate for solution for injection is also now licensed for this indication at a dose of 6mg IV over 1hour every 3-4 weeks. Doses should be reduced in renal impairment (creatinine clearance <30ml/min).

Bondronat® (Roche 0800 3281629)
Tablets 50mg, 28 days @ 50mg daily = £195.
Injection 1mg/ml, 6mg vial = £195.

iii) Liposomal cytarabine injection

Liposomal cytarabine injection (Depocyte®) has recently been launched. It is indicated for the treatment of lymphomatous meningitis via intrathecal injection. The injection is available as a 50mg suspension in 5ml, and costs £1250. For further information, contact medical information at Napp Pharmaceuticals (01223 424444).

iv) Flurbiprofen suppositories

Flurbiprofen 100mg suppositories (Froben®, Abbott 01628 773355) have been discontinued. Flurbiprofen 50mg and 100mg tablets remain (see flurbiprofen monograph).

May 2004

i) Paracetamol IV

An intravenous (IV) formulation of paracetamol has been launched for the short-term treatment of pain and/or fever when the IV route is required for urgent treatment and/or other routes of administration are unsuitable. The dose for adults and adolescents weighing >50kg is 1g, given over 15min, at intervals of at least 4 hours. For adults and adolescents weighing <50kg, the dose is 15mg/kg/dose, up to a daily maximum of 60mg/kg or 4g (whichever is the smaller).

Perfalgan® (Bristol-Myers Squibb 020 8754 3769)
Injection 1g/100 ml, 100ml = £1.50.

June/July 2004

i) Oxycodone capsules, injection and tablets m/r (OxyNorm®/OxyContin®, Napp Pharmaceuticals 01223 424444) are now licensed for use in severe non-cancer pain. Full details can be found in the relevant SPCs.

ii) Nefopam hydrochloride injection 20mg/ml (Acupan®, 3M Healthcare 01509 611611) has been discontinued. There is no alternative UK supplier.

iii) Sodium clodronate 400mg capsules (Loron®, Roche 0800 328 1629) have been discontinued. The 520mg tablet is still available (note: one 520mg tablet is equivalent to two 400mg capsules in terms of efficacy). Sodium clodronate 400mg capsules and 800mg tablets (Bonefos®, Boehringer Ingelheim 01344 424600) remain available. Prices are unaltered (see bisphosphonates monograph for details).

iv) Thioridazine suspension 25mg/5ml, 100mg/5ml and syrup 25mg/5ml (Melleril®, Novartis 01276 692255) have been discontinued. A generic oral solution is still available from Hillcross or Rosemont.

Thioridazine (non-proprietary)
Oral solution 25mg (as thioridazine hydrochloride)/5ml, 28 days @ 25mg o.n. = £0.84.

v) Changes have been made to the ipratropium bromide metered dose inhaler (MDI) range. The 20microgram/dose MDI is now CFC-free. The 40microgram/dose MDI (Atrovent Forte®) and 20microgram/dose Autohaler® have been discontinued. Suggested alternatives are below.

Atrovent® (Boehringer Ingelheim 01344 424600)

Aerosol inhalation 20microgram/metered inhalation (CFC-free), 28 days @ 40microgram (2 puffs) q.d.s. = £4.72.
Dry powder capsules (for use in Aerohaler®) 40microgram, 28 days @ 40microgram q.d.s. = £11.79. A pack containing an Aerohaler® plus 100 dry powder capsules costs £14.53.

vi) The SPC for cefradine capsules and syrup (Velosef®, Bristol-Myers Squibb 020 8572 7422) contains new cautions and contra-indications. Concurrent use with a loop diuretic may increase cefradine nephrotoxicity. Probenecid may raise serum cefradine levels by reducing renal clearance. Newly included side effects are dizziness, headache, pruritus, fever and reversible interstitial nephritis. Further, cefradine should not be used in porphyria. For a full list of cautions and contra-indications, see the SPC.

August 2004

i) Pregabalin for neuropathic pain

Pregabalin (Lyrica®, Pfizer 01304 616161), 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) Sustained release epidural injection of morphine

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 end 2004 and a licensing application has also been submitted to the MHRA in the UK.

iii) Diamorphine ampoule break seals

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

iv) Olanzapine and risperidone in dementia

The SPCs for olanzapine (Zyprexa®, Lilly 01256 315999) and risperidone (Risperdal®, Janssen-Cilag 01494 567567) 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 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.

v) Macrogol 3350 for chronic constipation

Macrogol 3350 (Movicol®, Norgine 01895 826600) 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.

vi) Use of salicylates with sodium valproate

The SPC for sodium valproate (Epilim®, Epilim IV® and Epilim Chrono®, Sanofi-Synthelabo 01483 505515) 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.

vii) 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) Anticipated shortage of dexamethasone 0.5mg tablets

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).

ii) Phenobarbital 200mg/ml injection

Concord Pharmaceuticals (0845 602 0137) has discontinued phenobarbital 200mg/ml injection (Gardenal®).

Alternative supplies can be obtained from Martindale Pharmaceuticals (01277 266600).

iii) Medroxyprogesterone acetate tablets (Farlutal®)

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.

iv) Thioridazine 50 and 100mg tablets
Novartis (01276 692255) has discontinued the 50 and 100mg strengths of thioridazine tablets (Melleril®). The 10 and 25mg strengths can still be obtained.

Generic alternatives are available.

v) Phenytoin 50mg tablets

APS/Berk (01323 501111) has discontinued phenytoin 50mg tablets. Phenytoin 50mg capsules remain available.

October 2004

a) New and discontinued products and changes to existing UK products
i) Pregabalin released in the community

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 newsletter.

Lyrica® (Pfizer 01304 616161)
Capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 300mg, 28 days @ 300mg o.d. = £32.20.

ii) Duloxetine

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).

iii) Fletcher's Enemette

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.

iv) Domperidone SPC change

The SPC for domperidone (Motilium®, Sanofi-Synthelabo 01483 505515) 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.

b) Palliative care prescribing changes in September 2004 BNF 48

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 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.

November/December 2004

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