Part IV

Palliativedrugs.com Newsletter Summary

Discontinued preparation since July 2003

New products since July 2003

Changes to continuing products

Discontinued Preparations

What follows is selective; for all the information given on a month-by-month basis in the Newsletter, visit the website: www.palliativedrugs.com

July 2003

1. ***Dextromoramide***
2. ***Salivace***

January 2004

1. ***Morphine sulphate (Sevredol®) oral solution 10mg/5ml and 20mg/ml***

Both strengths of *alcohol-free* morphine sulphate (Sevredol®) oral solution have been discontinued. 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*).

2. ***Piroxicam 20mg suppositories***
3. ***Metoclopramide 5mg tablets***

March 2004

Venlafaxine 50mg tablets

April 2004

1. ***Mirtazapine non-dispersible tablets***

Following the launch of mirtazapine orodispersible tablets (Zispin® SolTab), the original mirtazapine tablets (Zispin®) are being discontinued. The new orodispersible tablets (15mg, 30mg and 45mg) are bio-equivalent to the original non-dispersible tablets.

2. ***Flurbiprofen suppositories***

New Products

July 2003
Morphgesic SR

Morphine sulphate m/r tablets available as 10mg, 30mg, 60mg and 100mg for q12h administration (Morphgesic SR, Amdipharm 0870 777 7675).
Cost for 28 days @100mg b.d. = £28.28.

August 2003
Nabilone

Nabilone capsules 500microgram and 2mg have been launched *on a named patient basis* (Cambridge Laboratories 0191 2969).
Cost of 500microgram capsules x20 = £68.94; 2mg capsules x20 = £228.80.
For more information about nabilone and named patient prescribing, see www.palliativedrugs.com

November/December 2003
1. Orodispersible mirtazapine

An orodispersible mirtazapine 30mg tablet (Zispin SolTab) which dissolves on the tongue without water is now available. Although the tablets disperse completely in water, the company have no information on their 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 30mg, 28 days @30mg o.n = £19.25.

2. Methadone hydrochloride injection 25mg/ml & 50mg/ml

Methadone hydrochloride injection 25mg/ml (2ml ampoule) and 50mg/ml (1ml ampoule) are now available for IV, IM and SC use, licensed for the management of withdrawal in opioid addiction. Both cost £2.05 per ampoule and are available as **Synastone**, Auden McKenzie 020 8900 2122.

February 2004
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/sublingual 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).

March 2004

1. 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.

2. Orodispersible mirtazapine

Following our report in the November/December newsletter surrounding the launch of an orodispersible mirtazapine 30mg tablet (Zispin SolTab). The company have 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.

April 2004

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.

May 2004

IV paracetamol

An intravenous (IV) formulation of paracetamol has been launched for the short-term treatment of pain and/or fever when other routes of administration are unsuitable. The dose for adults and adolescents weighing >50kg is 1g, *given over 15min*, at intervals of at least 4h. For adults and adolescents weighing <50kg, the dose is 15mg/kg/dose. A maximum of 4 doses in 24h is recommended.

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

Changes to products

July 2003

1. Dexamethasone labelling

The UK Medicines Control Agency (MCA) has advised Organon Laboratories (01223 432700) to alter the labelling on their dexamethasone injectable products to accurately express the amount of dexamethasone in relation to the base and the salt forms.

Dexamethasone injection can be formulated as dexamethasone *phosphate* or dexamethasone *sodium phosphate*. The Organon brand is formulated as **dexamethasone sodium phosphate** 5mg in 1ml. Traditionally the dose of the Organon brand has been prescribed as dexamethasone *base*. The product label used to express the amount of dexamethasone base as an *approximation*. The product has not changed, only the label in order to accurately reflect the amount of dexamethasone *base*:

For dexamethasone sodium phosphate 5mg in 1ml ampoule
Old label 'equivalent to dexamethasone 4mg in 1ml (approx)'
New label 'each ml contains dexamethasone 3.8mg'

For dexamethasone sodium phosphate 10mg in 2ml vial
Old label 'equivalent to dexamethasone 8mg in 2ml (approx)'
New label 'each ml contains dexamethasone 3.8mg'.

Some hospitals are resolving this situation by overlabelling the injection so that a 1ml and 2ml volume are still given for doses of dexamethasone base of 4mg and 8mg respectively.

There is another injectable dexamethasone in the UK from Mayne Pharma (01926 820820). This is a different concentration, and is also expressed and *prescribed* as a different salt, i.e. **dexamethasone phosphate** 4mg in 1ml. This has caused confusion when changing between different preparations. A table which can be downloaded as a pdf (by right clicking etc.) summarises products available in the UK, and the dexamethasone base and salt content.

2. Etamsylate

The entry in the current British National Formulary (BNF 45) on page ix stating the discontinuation of etamsylate (Dicynene) is *incorrect*. Etamsylate tablets are still available in the UK. The injection was discontinued in October 2002, however it can be obtained via IDIS (020 8410 0710).

3. Thalidomide

The license and distribution of thalidomide 50mg capsules has changed from Penn pharmaceuticals to Pharmion. The 100mg capsules are no longer available. The supply from this company requires registration of the patient, pharmacist and prescriber by the Pharmion Risk Management Programme (PRMP). Once all three parties are registered, the prescriber has to obtain an authorisation number and the pharmacist a confirmation number directly from the company for each monthly prescription. The patient and prescriber also have to complete a mandatory monthly telephone survey. Further details including patient and healthcare information packs and an SPC can be obtained from the Pharmion Risk Management Centre (0808 156 3059) or via the PRMP website www.prmp.com.

Thalidomide tablets 25mg, 50mg and 100mg can be obtained via IDIS (020 8410 0710) on a named patient basis. Supply requires details of the patient, pharmacist and prescriber for every order.

October 2003
Levomepromazine and prolonged QT interval: SPC change

Special warnings and precautions for use
As with other neuroleptics, cases of QT interval prolongation have been reported with levomepromazine very rarely. Consequently, and if the clinical situation permits, absence of the following risk factors for onset of this type of arrhythmia should be verified prior to administration:

- bradycardia or 2nd or 3rd degree heart block
- metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesaemia starvation or alcohol abuse
- a history of QT interval prolongation, ventricular arrhythmias or Torsades de Pointes
- a family history of QT interval prolongation
- ongoing treatment with another drug liable to induce marked bradycardia, hypokalaemia, slowed intracardiac conduction or prolonged QT interval.

It is recommended, as part of the initial evaluation in patients to be treated with levomepromazine, that an ECG is performed with measurement of serum calcium, magnesium and potassium levels. Periodic serum electrolyte levels should be monitored and corrected especially when long-term chronic usage is anticipated. An ECG should be repeated to assess the QT interval whenever dose escalation is proposed and when the maximum therapeutic dose is reached.

Interactions with other medicaments and other forms of interaction
There is an increased risk of arrhythmias when neuroleptics are used with drugs that prolong the QT interval such as certain anti-arrhythmics, antidepressants and other antipsychotics. If these drugs are co-administered this should be done with ECG monitoring.

Undesirable effects
Very rarely cases of Torsades de Pointes have been reported, treatment of which should include discontinuation of levomepromazine and correction of hypoxia, electrolyte abnormalities and acid base disturbances.

This type of clause already appears in the SPCs of other antipsychotics, e.g. haloperidol, prochlorperazine and chlorpromazine and is likely to appear in the SPCs of even more antipsychotics as they come up for their 5-year marketing renewal.

Reports of Torsades de Pointes generally relate to psychiatric patients receiving much larger doses than are generally used in palliative care. For levomepromazine, between 1957-2001, there were 37 reports of any form of cardiac toxicity out of an estimated 5.5 million patients receiving an average daily dose of 100mg. Further, in a survey of 300 palliative care patients, although 16% of patients had prolonged QTc, seriously prolonged QT was present in only 2 patients (with co-existing ischaemic heart disease).[1]

1. Walker G *et al* (2003) Prolongation of the QT interval in palliative care patients. *Journal Pain Symptom Management*. **26**:855-9. Pubmed abstract of this paper
See also Appendix 3: Prolongation of the QT interval in palliative care

Nov/Dec 2003

1. Erratum in Palliative Care Formulary 2

There is a mistake in the syringe driver section of PCF2 CD-ROM and book (but not on the website); on p.301 under 'Drug compatibility' and on p.302 under 'Infusion site problems'. The concentration of diamorphine should read **>40-50mg/ml,** *not* >450mg/ml.

2. Buprenorphine (Transtec) dose calculator

At the 2003 Advanced Courses in Pain and Symptom Management, we highlighted the possible confusion caused by the Transtec *dose calculators*. We can now confirm that Napp have added the following words for clarification:

'A guide to the initial dose when transferring patients to Transtec patches. Not intended to show equivalent doses between other pairs of opioids.'

New *dose calculators* are available from Napp Pharmaceuticals or from the local company representative.

March 2004

1. Zoledronic acid infusion

In future, 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.

2. Thalidomide supply in UK

IDIS are unable to import thalidomide (Lipomed brand) pending a legal dispute. Until this is resolved, supplies of thalidomide can be obtained via Pharmion using their risk management programme (contact 0808 156 3059) or visit the website www.prmp.com.

A recent article in the Pharmaceutical Journal summarises the history and use of risk management programmes in relation to thalidomide: Pharmaceutical Journal 272: 190-191 and correpondence Pharmaceutical Journal 272: 278-279.

April 2004

1. Thalidomide update

All tablet strengths (25, 50, 100mg) of the Myrin brand of Thalidomide (Lipomed, Switzerland) can be purchased through an independent importer in London: Alan Pharmaceuticals (telephone 020 8346 4311, fax 020 8346 5218, e-mail info@thalidomide.co.uk).

2. SSRIs

The Committee on the Safety of Medicines (CSM) has advised that citalopram, escitalopram, fluvoxamine, paroxetine and sertraline, as well as venlafaxine, should *not* be used to treat depression in those under 18 years because of an increased risk of self-harm and suicide.

3. Maximum dose of rectal diazepam for seizures

Not more than 30mg (15mg in elderly) should be administered PR. This can be repeated after 12h.

May 2004
Atypical antipsychotics & the risk of stroke

The UK Committee for the Safety of Medicines (CSM) has analysed data from RCTs in people with dementia and found an approximate 3-fold increased risk of cerebrovascular adverse events (including CVAs and TIAs) with olanzapine (Zyprexa®) and risperidone (Risperdal®) *compared to placebo*. The reason for this increased risk is unknown.

For risperidone, estimates of numbers of patients needed to be treated for one year to produce one attributable cerebrovascular adverse event ranged from 4-14. As a result, CSM has advised that risperidone and olanzapine should not be used for behavioural symptoms of dementia.

- the use of risperidone for acute psychosis in elderly patients with dementia should be short-term and under specialist advice (the SPC for olanzapine says it is not recommended for dementia-related psychosis)
- patients with dementia who are currently being treated with an atypical antipyschotic drug should have their treatment reviewed.

The CSM recommends that olanzapine and risperidone be used with caution in patients with risk factors for cerebrovascular disease (e.g. previous CVA or TIA, hypertension, diabetes mellitus, current smoking, atrial fibrillation). The treatment of psychosis in people without dementia and with no history of CVA or TIA is unaffected by the CSM restriction.

The CSM also warns of potentially similar risks with quetiapine. Further data is awaited from analysis of the General Practice Research Database, examining CVA in elderly people with dementia in primary care exposed to risperidone compared to other antipsychotics. At present*, it is not known whether there is a similar risk with the older typical antipsychotics.*

Canadian and USA licensing authorities have also issued safety alerts. Further information can be obtained from the company medical information departments:

- olanzapine (Janssen-Cilag 0800 731 8450)
- risperidone (Lilly 01256 315000).

However, it has been claimed that some patients may suffer as a result of the restriction (Mowat et al 2004 BMJ 328: 1262). Reference is made to a study currently ‘in press’ which is said to demonstrate that there are no excess strokes in elderly patients receiving atypical antipsychotics compared with typical antipsychotics. However, the authors of the letter do not refer specifically to dementia, nor does the title of the unpublished article include the word.