NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 5; Number 7 **April 2011**

What's new this month:

- **Rasagiline (Azilect) is re-classified as AMBER as a second line alternative to selegiline in patients with Parkinson's Disease (see page 3).**
- **Fenticonazole (Ginoxin) vaginal capsules and cream are designated GREEN as an alternative to clotrimazole in the topical treatment of vaginal candidiasis (see page 6).**
- **A new range of combined oral contraceptives offer significant savings in comparison to established brands (see page 6).**
- **NICE guidance on prucalopride in the treatment of chronic constipation in women is reviewed (see page 8).**

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This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: FEBRUARY 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Amifampridine phosphate (Firdapse) tablets	Licensed for the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults up to a maximum daily dose of 60mg.	RED-RED Unlicensed lower cost 3,4-diaminopyridine preparations are designated AMBER (for specialist initiation only)
Ethinyloestradiol 20mcg/desogestrel 150mcg (Gedarel 20/150)	Combined oral contraceptive	GREEN Should be used in preference to Mercilon first line
Ethinyloestradiol 30mcg/ desogestrel 150mcg (Gedarel 30/150)	Combined oral contraceptive	GREEN Should be used in preference to Marvelon first line
Ethinyloestradiol 20mcg/ gestodene 75mcg (Millinette 20/75)	Combined oral contraceptive	GREEN Should be used in preference to Femodette and Sunya first line
Ethinyloestradiol 30mcg/gestodene 75mcg (Millinette 30/75)	Combined oral contraceptive	GREEN Should be used in preference to Femodene and Katya first line
Ethinyloestradiol 30mcg/ levonorgestrel 150mcg (Rigevidon)	Combined oral contraceptive	GREEN Should be used in preference to Microgynon 30 and Ovranette first line
Ethinyloestradiol/ levonorgestrel triphasic pill (TriRegol)	Combined oral contraceptive	GREEN Should be used in preference to Logynon first line
Fenticonazole (Ginoxin) vaginal capsules 200mg, 600mg and 2% vaginal cream	A new topical imidazole antifungal agent licensed for the treatment of vaginal candidiasis	GREEN
Imatinib (Glivec) tablets	Licensed for the treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours (GIST)	RED Doses above 400mg once daily are no longer recommended for this indication
Pigmanorm cream	An unlicensed product used for the treatment of melanin-induced hyperpigmentation of the skin	RED
Prucalopride (Resolor) tablets	Licensed for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.	AMBER No shared care guideline required. Third line. Should only be initiated by a clinician with experience in treating chronic constipation.
Rasagiline (Azilect) tablets	Licensed for the treatment of Parkinson's disease used alone or as an adjunct to levodopa with dopa-decarboxylase inhibitor	AMBER No shared care guideline required. Second line after selegiline. Limited role as an alternative to selegiline.
Temsirolimus (Torisel) intravenous infusion	Licensed for the treatment of relapsed or refractory mantle cell lymphoma	RED-RED
Trastuzumab (Herceptin) intravenous infusion	Licensed in combination with cisplatin and capecitabine or 5FU for metastatic gastric cancer in patients with HER2-positive tumours who have not received treatment for metastatic gastric cancer	RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

REVIEW: RASAGILINE (AZILECT) TABLETS

Rasagiline (Azilect) is a selective, irreversible inhibitor of monoamine-oxidase- B (MAO-B). This enzyme is found in the neurons of the hypothalamus and is responsible for the metabolism of dopamine. Inhibition of MAO-B is thought to help conserve dopamine supplies and therefore delay the need for levodopa therapy for the treatment of Parkinson's disease; it is also thought to enable the use of lower doses of levodopa in patients with advanced disease. There are currently two MAO-B inhibitors available in the UK: rasagiline and selegiline (generic/Eldepryl/Zelapar).

Rasagiline (Azilect) is licensed for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations. Both PACEF and ULH Drug and Therapeutics Committee reviewed rasagiline in 2008 and found no evidence to suggest that it was superior in efficacy to selegiline. Since this decision, a number of new trials have been published and PACEF were asked to review this new evidence.

The ADAGIO trial examines the possibility that rasagiline has disease-modifying effects in PD. 1,176 patients with untreated PD were randomised to rasagiline 1mg or 2mg/day for 72 weeks (early-start group) or placebo for 36 weeks followed by rasagiline 1mg or 2mg/day for 36 weeks (delayed-start group). **Early treatment with rasagiline at a dose of 1mg/day was shown to produce benefits consistent with a possible disease-modifying effect; these benefits were not shown by the 2mg/day dose.**

In the TEMPO trial, 404 patients with early stage PD were randomised to 1mg (134pts), 2mg (132 pts) or placebo (138 pts). At 26 weeks, the rasagiline groups continued on their dose of rasagiline for a further 26 weeks; patients on placebo were initiated on rasagiline 2mg at this point. Results showed that patients who received placebo during the first 26 week phase demonstrated a greater functional decline than those in the active treatment groups throughout. **The authors of the study suggest that this represents a possible neuroprotective effect of rasagiline**; longer term blinded studies would be required to confirm or refute this.

LARGO is an 18 week randomised controlled trial (RCT) in which 687patients with advanced PD on at least three and not more than eight doses of levodopa a day were randomised to rasagiline 1mg (231 pts) or entacapone 200mg (227 pts) or placebo (229 pts). The study showed comparable clinical efficacy between rasagiline and entacapone. **There are no comparative trials between rasagiline and selegiline.**

The adverse effect profile is similar between the two MAO-Bs with both causing a wide range of adverse effects. However, unlike selegiline, rasagiline is not converted into amphetamine metabolites. In theory this should result in a lower incidence of certain adverse effects (e.g. hallucinations, sleep disorders, anorexia etc), although this has yet to be confirmed in clinical practice. The manufacturers of selegiline caution against the use of the drug in patients with uncontrolled hypertension, arrythmias, angina and psychosis on the basis of the risk of elevated levels of

amphetamine metabolites; this is less of a risk with rasagiline. In addition, the use of selegiline in the elderly carries a risk of initial confusion and agitation, necessitating careful initial titration from a 2.5mg dose. Rasagiline may present a preferable alternative in the frail elderly and those with a history of falls or dizzy spells.

A cost comparison between the two drugs reveals the following:

Drug	Dose	28 day treatment cost
Rasagiline 1mg tablets (Azilect)	**1mg daily**	**£70.72**
Selegiline 5mg tablets (generic)	5mg at breakfast and mid-day	£5.13
Selegiline 10mg tablets (generic)	10mg in the morning	£6.84
Selegiline 5mg tablets (Eldepryl)	5mg at breakfast and mid-day	£9.25
Selegiline 10mg tablets (Eldepryl)	10mg in the morning	£9.03
Selegiline 1.25mg tablet (as oral lyophilisate) (Zelapar)	1.25mg daily before breakfast (equivalent to 10mg conventional selegiline)	£40.03

The high comparative cost of rasagiline means that selegiline should always be considered as the preferred first line choice. However, certain patient groups at particular risk of selegiline related adverse effects may be better managed with rasagiline.

PACEF Recommendation:
Early indications suggest that rasagiline has possible disease-modifying and neuroprotective effects when used in the treatment of PD. Amphetamine-like metabolites resulting from selegiline treatment can increase cardiovascular risk in patients with hypertension or cardiovascular disease. In addition, selegiline can cause confusion and agitation, particularly in the early stages of treatment and can be problematic in the frail elderly or in those with a history of falls, dizzy spells or psychosis. Rasagiline is metabolised differently to selegiline and can be considered as an appropriate alternative in these patient groups. Inconsistent trial results, lack of comparative data, high comparative cost and uncertainty about whether theoretical advantages translate into real clinical benefits make it difficult for PACEF to justify rasagiline as a first line treatment for PD at this time. Nonetheless, rasagiline (Azilect) is approved as a second line alternative to selegiline. Designation: AMBER. All initiations should be by a specialist; no shared care guideline is required. Rasagiline should be confined to use in those with hypertension or cardiovascular disease; it may also be preferred to selegiline in patients who are frail or have a history of falls, dizzy spells or psychosis. The possible disease-modifying and neuroprotective effects of rasagiline may also make it a preferred option in very young patients presenting with PD.

NEW DRUG ASSESSMENT: AMIFAMPRIDINE PHOSPHATE TABLETS (FIRDAPSE)

Amifampridine phosphate (Firdapse) has been licensed as an orphan drug for the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults up to a maximum daily dose of 60mg. LEMS is a rare autoimmune neuromuscular disorder with a prevalence of about 5 per 2,000,000 population. It is characterized by muscle weakness and fatigability and symptoms of autonomic dysfunction. LEMS is strongly associated with cancer, especially small-cell lung cancer (SCLC). It is estimated that about 3% of patients with SCLC have LEMS, and 40 to 60% of patients with LEMS have SCLC and 5% have other cancers. Amifampridine is the international non-

proprietary name for 3,4 diaminopyridine (3,4-DAP). Previously only unlicensed formulations of 3,4-DAP base have been available.

Unlicensed 3,4 -DAP has been in clinical use since the early 1980s. Three small randomised placebo controlled trials have shown it to be effective in the symptomatic treatment of LEMS, although the overall quality of the evidence base is poor. No new clinical trials were conducted to support the license application for Firdapse, with all evidence obtained from the existing published trials pertaining to amifampridine.

Unpublished data submitted to the European Medicines Agency (EMA) has shown similar bioavailability of the phosphate salt (Firdapse) compared with the base formulation (3,4-DAP) in a single-dose crossover study in 26 healthy volunteers. Since the introduction of the licensed product, a number of suppliers have decided to stop supplying the unlicensed form. This has made it increasingly difficult to obtain supplies of unlicensed 3,4-DAP; hospital pharmacists, community pharmacists and dispensing GPs attempting to order supplies are now required to provide written evidence confirming why the unlicensed product is required.

Unlicensed 3,4-DAP currently generates prescribing costs of between £1,500 and £2,200 per patient per year; it has been estimated that replacing unlicensed 3,4-DAP with Firdapse would increase drug costs to £30,000 - £45,000 per patient per year.

PACEF Recommendation:
Standard advice from the Medicines and Healthcare products Regulatory Agency (MHRA) is that licensed products should be prescribed and dispensed where indicated and where available. Where a licensed product is not available, an unlicensed alternative can be prescribed and dispensed. The financial implications of this advice for PCTs, Acute Trusts and emerging GP Commissioning Consortia could be grave if the current trend for manufacturers to market expensive branded orphan drugs in competition with lower cost unlicensed equivalents continues. East Midlands Specialised Commissioning Group (EMSCG) have confirmed their intention to commission only low cost unlicensed 3,4-DAP for the treatment of LEMS in the future and are working to formalise this through a locally agreed commissioning policy. In the interim, unlicensed 3.4-DAP preparations are designated AMBER (for specialist initiation only) and amifampridine phosphate tablets (Firdapse) are designated RED/RED. Any requests for initiation of FIRDAPSE tablets should be referred through the individual funding requests process until EMSCG policy has been ratified. This decision will be revised in response to EMSCG final policy. Community pharmacies and dispensing practices can be reassured that PACEF are entirely in support of the continued supply of unlicensed 3,4-DAP to these patients despite the fact that a licensed equivalent is now available. Additional support in the form of an East Midlands Specialised Commissioning policy will appear shortly.

RAPID DRUG ASSESSMENT: PIGMANORM CREAM

Pigmanorm cream is an unlicensed imported product used for the treatment of melanin-induced hyperpigmentation of the skin (e.g. melasma and hyperpigmentations following inflammation). Each gram of cream contains hydroquinone 50mg (5%), tretinoin 1mg (0.1%) and hydrocortisone 10mg (1%).

Hydroquinone is an effective skin lightening agent. It increases melanin excretion from melanocytes and may also prevent its production. Tretinoin is used to enhance

the efficacy of hydroquinone by increasing its penetration into the skin. It may also have a direct effect in reducing melanisation. Hydrocortisone is a weak anti-inflammatory corticosteroid which causes some transient bleaching and has an anti-irritant effect.

Creams containing hydroquinone 5%, hydrocortisone 1% and tretinoin 0.1% in aqueous cream are on the list of preferred unlicensed dermatological preparations (Specials) 2008 produced by the British Association of Dermatologists. Skin lightening creams containing similar ingredients have been used for many years.

PACEF Recommendation:
Pigmanorm cream, or equivalent triple component formulations, has an established role as a skin lightening cream. However, the unlicensed status of the product and potential difficulties in sourcing supplies could create problems with prescribing and dispensing in primary care. As a result of this, Pigmanorm cream is designated RED. All prescribing and supply should be undertaken by ULHT dermatologists. Any requests to GPs to prescribe should be refused and referred back to the initiating dermatologist.

RAPID DRUG ASSESSMENT: FENTICONAZOLE (GINOXIN) VAGINAL CAPSULES 200MG, 600MG AND 2% VAGINAL CREAM

Fenticonazole (Ginoxin) is a new imidazole antifungal agent licensed for the treatment of vaginal candidiasis. Evidence from three small published comparator trials suggests that fenticonazole and clotrimazole are comparable in terms of cure rates for the treatment of vaginal candidiasis. UK national guidance produced by the British Association of Sexual Health (BASH) considers all of the topical imidazoles as being broadly comparable, offering cure rates of 80% or over in uncomplicated acute vulvovaginal candidias. A cost comparison reveals that fenticonazole products are 16 to 33% lower in cost than equivalent clotrimazole (Canestan) formulations. If fenticonazole replaced clotrimazole as the preferred topical imidazole in Lincolnshire the potential saving would be approximately £3,300pa.

PACEF Recommendation:
PACEF are convinced that fenticonazole offers an effective alternative to clotrimazole in the treatment of vaginal candidiasis. The clotrimazole (Canestan) range is widely prescribed and purchased over-the-county (OTC) in Lincolnshire and remains the preferred first line choice in local prescribing policy. The availability of the combination pack (Canestan combi) and the ability to purchase clotrimazole products OTC from community pharmacies gives clotrimazole a significant advantage over fenticonazole. Cost comparison reveals a small saving from the wider utilisation of fenticonazole. As a result of this, fenticonazole (Ginoxin) vaginal capsules 200mg, 600mg and 2% vaginal cream are designated GREEN.

RAPID DRUG ASSESSMENT: RIGEVIDON, GEDAREL 20/150, GEDAREL 30/150, MILLINETTE 20/75, MILLINETTE 30/75 AND TRIREGOL

Consilent have launched a range of combined oral contraceptives (COCs) that are equivalent to established brands and are priced approximately 25% lower. A cost comparison reveals the price differences:

Combined Pill	Cost (£) per 3x21 pack
Ethinyloestradiol 30mcg/levonorgestrel 150mcg	
Rigevidon	£1.89
Microgynon 30	£2.82
Ovranette	£2.20
Ethinyloestradiol 20mcg/desogestrel 150mcg	
Gedarel 20/150	£5.98
Mercilon	£7.67
Ethinyloestradiol 30mcg/desogestrel 150mcg	
Gedarel 30/150	£4.93
Marvelon	£6.45
Ethinyloestradiol 20mcg/gestodene 75mcg	
Millinette 20/75	£6.37
Femodette	£8.85
Sunya	£6.62
Ethinyloestradiol 30mcg/gestodene 75mcg	
Millinette 30/75	£4.85
Femodene	£6.73
Katya	£5.03
Triphasic ethinyloestradiol levonorgestrel 30/50 (6 tabs) 40/75 (5 tabs) 30/125 (10 tabs)	
TriRegol	£2.87
Logynon	£3.82

There are potential savings of £60,500pa if all of the COCs listed were prescribed as the Consilient brand.

PACEF Recommendation:
Rigevidon, Gedarel 20/150, Gedarel 30/150, Millinette 20/75, Millinette 30/75 and TriRegol are all designated GREEN and should be considered as first line choices for all new patients requiring combined oral contraception. Individual practices or GP Commissioning Consortia should consider therapeutic switching of equivalent products to release further savings.

NICE TECHNOLOGY APPRAISAL 207: *TEMSIROLIMUS FOR THE TREATMENT OF RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA* (TERMINATED APPRAISAL) (OCTOBER 2010)

NICE was unable to recommend the use of temsirolimus within the NHS for the treatment of relapsed or refractory mantle cell lymphoma because no evidence submission was received from the manufacturer or sponsor of the technology.

PACEF Recommendation:
Temsirolimus (Torisel) intravenous infusion is designated RED-RED for the treatment of relapsed or refractory mantle cell lymphoma.

NICE TECHNOLOGY APPRAISAL 208: *TRASTUZUMAB FOR THE TREATMENT OF HER2-POSITIVE METASTATIC GASTRIC CANCER* (NOVEMBER 2010)

Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil (5FU), is recommended as an option for the treatment of people with human epidermal growth factor receptor 2 (HER2)-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:

- have not received prior treatment for their metastatic disease and

- have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).

PACEF Recommendation:
Trastuzumab intravenous infusion (Herceptin) in combination with cisplatin and capecitabine or 5FU for metastatic gastric cancer in patients with HER2-positive tumours is designated RED subject to NICE criteria.

NICE TECHNOLOGY APPRAISAL 209: *IMATINIB FOR THE TREATMENT OF UNRESECTABLE AND/OR METASTATIC GASTROINTESTINAL STROMAL TUMOURS* (NOVEMBER 2010)

Imatinib at 600 or 800 mg/day is not recommended for people with unresectable and/or metastatic gastrointestinal stromal tumours whose disease has progressed after treatment with 400 mg/day imatinib.

PACEF Recommendation:
Imatinib (Glivec) tablets are designated RED for unresectable and/or metastatic gastrointestinal stromal tumours. Doses above 400mg once daily are not recommended for this indication.

NICE TECHNOLOGY APPRAISAL 211: *PRUCALOPRIDE FOR THE TREATMENT OF CHRONIC CONSTIPATION IN WOMEN* (DECEMBER 2010)

NICE Recommendations

1. Prucalopride is recommended as an option for the treatment of chronic constipation only in women for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered.
2. If treatment with prucalopride is not effective after 4 weeks, the woman should be re-examined and the benefit of continuing treatment reconsidered.
3. Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has carefully reviewed the woman's previous courses of laxative treatments.

Further information

Prucalopride (Resolor) is a selective 5HT4 receptor agonist that predominantly stimulates colonic motility. It is licensed for the 'symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief'. It is not currently licensed in men as approximately 90% of participants in the key trials were women.

The evidence reviewed by NICE comes from three 12 week placebo controlled randomised controlled trials (RCTs) in 1691 patients with a history of chronic constipation (average no more than 2 spontaneous, complete bowel movements [SCBM] per week for at least 6 months prior to study entry, but not necessarily refractory to other laxatives). Patients were randomised to receive prucalopride 2mg or 4mg (unlicensed dose) or placebo, all once daily. Rescue laxative medication was available to all participants. Pooled data from these studies demonstrated that prucalopride was more effective than placebo at achieving the primary outcome of 3 or more SCBM per week. However, response rates were low with relatively few

participants responding to treatment (i.e. at the licensed dose of 2mg, 24% of patients achieved 3 or more SCBM per week compared to 11% on placebo).

A similar 4 week placebo controlled RCT (n=305) compared prucalopride 1mg, 2mg or 4mg once daily with placebo in patients aged over 65 years (mean age 76 years) with chronic constipation. The proportion of people who had an average of 3 or more SCBM per week was 40% for 1mg and 32% for 2mg compared with 20% for placebo. There are no long term placebo-controlled studies assessing the efficacy or safety of prucalopride. Prucalopride has not been compared in any trial with an active comparator.

The most common adverse effects seen with prucalopride were headache, abdominal pain, nausea and diarrhoea. These generally occurred within the first few days of treatment and thereafter the incidence of these symptoms was similar to placebo.

The European Medicines Agency notes that certain 5HT4 agonists such as cisapride induce QT interval prolongation which in some instances leads to ventricular arrhythmias and sudden death. Short term data indicate that prucalopride has a negligible influence on the QT interval. Palpitations were recorded in 0.7% of study participants who received placebo, 1% of those receiving 1mg daily, 0.7% of those receiving 2mg and 1.9% of those receiving 4mg once daily. The manufacturers' SPC advises that prucalopride should be used with caution in patients with a history of arrhythmias or ischaemic heart disease.

Cost comparison

	Daily dose range	**Cost / 28 days**
Prucalopride 1mg or 2mg tabs	**1mg – 2mg once daily**	**£38.69 - £59.52***
Ispaghula 3.5g sachets (Fybogel)	1 sachet twice daily	£3.44
Docusate 100mg caps	Up to 500mg daily	£8.96
Bisacodyl EC tabs 5mg	5 – 10mg at night	£0.92 - £1.83
Bisacodyl suppositories	10mg in the morning	£2.52
Senna tablets	2 – 4 at night	£1.47 - £2.93
Lactulose solution	15ml twice daily	£5.69 (using 300ml pack size) £4.17 (using 500ml pack size)
Movicol sachets	1 – 3 sachets daily, usually for up to 2 weeks	£6.23 - £18.70
Laxido sachets		£4.98 - £14.95

*The manufacturer estimated that the annual cost of treatment with prucalopride is £622 for adult women and £403 for older women, assuming that each woman receives treatment for an average of 220 days each year.

What is the place of prucalopride in the treatment of constipation?

A recent *MeReC Bulletin* on the management of constipation (Vol 21 No 2 (January 2011)) identified the following key steps:

- Advise about lifestyle measures (e.g. balanced diet, including dietary fibre, regular meals, adequate fluid intake, exercise).
- If dietary measures are ineffective after 4 weeks or while waiting for them to take effect, offer additional oral laxatives.
- Start treatment with a bulk forming laxative (soluble fibre) ensuring adequate fluid intake (e.g. ispaghula 3.5g sachets (Fybogel))

- If stools remain hard, add or switch to an osmotic laxative (e.g. lactulose solution, polyethylene glycol).
- If stools are soft but difficult to pass or if emptying is inadequate, add a stimulant laxative (e.g. bisacodyl EC tablets 5mg or senna tablets).
- Advise that laxatives can be stopped once the stool becomes soft and passes easily. Doses should be reduced in a gradual manner.
- In general, the smallest effective dose should be prescribed for the shortest time.
- Prolonged treatment with laxatives is seldom necessary (exceptions might be where there are medical causes, where a constipating drug cannot be stopped and in children when laxatives may be continued for several months to avoid relapse). Where long-term control of constipation is considered necessary, bulk forming laxatives are preferred.
- Only limited evidence supports the use of lactulose in chronic constipation. A Cochrane review concluded that polyethylene glycol (PEG) is superior to lactulose in terms of increasing stool frequency, improving stool form and reducing the need for additional products.

PACEF Comment:
Where polyethylene glycol is indicated, the Laxido brand of macrogol oral powder should be prescribed. The estimated saving across Lincolnshire primary care would be over £110,000pa if all prescribing for macrogol oral powder specified the Laxido brand.

- Stimulant laxatives should be considered before bulking agents where constipation results from lack of mobility (e.g. constipation in the elderly or disabled).
- In pregnancy, where dietary and lifestyle measures fail, bulking agents (soluble fibre) are preferred.
- Prucalopride has a role in women with chronic constipation for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered. It should only be initiated by a clinician with experience in treating chronic constipation.

PACEF Recommendation:
Prucalopride should be considered only where at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, have failed to provide adequate relief and invasive treatment for constipation is being considered. The exceptionally high cost of the product in comparison to all available alternatives and the weak evidence supporting its use means that it should only be considered third line and initiated only on the advice of a clinician with experience in treating chronic constipation (i.e. a consultant gastroenterologist, care of the elderly specialist or colorectal surgeon). As a result of this prucalopride (Resolor) is designated AMBER; no shared care guideline is required.

NICE CG 111: *NOCTURNAL ENURESIS – THE MANAGEMENT OF BEDWETTING IN CHILDREN AND YOUNG PEOPLE* (OCTOBER 2010)

NICE Recommendations

- Address excessive or insufficient fluid intake or abnormal toileting patterns before starting other treatment.
- Offer an alarm as the first-line treatment unless this is considered undesirable or inappropriate.

Desmopressin

- Offer desmopressin to children over 7 years if rapid onset and/or short-term improvement in bedwetting is the priority or an alarm is not suitable.
- Consider desmopressin for children aged 5-7 years if treatment is required.
- Explain the importance of fluid restriction from 1 hr before to 8 hrs after taking desmopressin.
- If there is no response after 1-2 weeks on a starting dose of 200mcg, increase the dose to 400mcg.
- Assess the response to desmopressin at 4 weeks and continue treatment for 3 months if there are signs of a response. Consider stopping if there are no signs of response.
- Consider continuing treatment with desmopressin for children and young people with bedwetting that has partially responded, as bedwetting may improve for up to 6 months after starting treatment.
- Withdraw desmopressin for one week every three months to assess response.
- Refer children and young people who have not responded to courses of treatment with an alarm and/or desmopressin.

Desmopressin combined with an anticholinergic

(NB Not all anticholinergics are licensed to treat nocturnal enuresis in children and young people)

- Consider if there is no response or a partial response to desmopressin treatment alone and the patient has been referred for further assessment.
- Consider if there are daytime symptoms in addition to bedwetting and the patient has been referred for assessment.

Imipramine

- Do not use as a first-line treatment for bedwetting in children and young people.
- Consider imipramine if there is no response to all other treatments and the patient has been referred for further assessment.
- Do not use combined with an anticholinergic.
- Review use every 3 months and withdraw imipramine gradually when stopping treatment.

A cost comparison of the licensed products reveals the following:

	Age	Dose	Cost for 28 days treatment
Desmopressin 200mcg tablets	5-18 years	200mcg at bedtime	£22.74
Desmopressin 200mcg tablets	5-18 years	400mcg at bedtime	£45.48
Desmopressin (as DesmoMelt)120mcg	5-18 years	120mcg at bedtime	£28.32
Desmopressin (as DesmoMelt) 240mcg	5-18 years	240mcg at bedtime	£56.63
Oxybutynin 2.5mg	5-12 years	2.5mg twice daily	£8.71
Oxybutynin 5mg	12-18 years	5mg three times daily	£12.19
Tolterodine 1mg	7-18 years	1mg at bedtime	£14.52
Imipramine 25mg	6-8 years	25mg at bedtime	£1.21
Imipramine 25mg	8-11 years	25-50mg at bedtime	£1.21-£2.42
Imipramine 25mg	11-18 years	50-75mg at bedtime	£2.42-£3.63

PACEF Recommendations:
Where desmopressin is indicated, standard 200mcg tablets are recommended first line.

NEW TRIALS IN BRIEF

STATINS FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

A Cochrane systematic review of 14 RCTs of statins involving 24,272 participants 10% or fewer of which had a history of CVD has been published and widely reported in the media. All cause mortality, combined fatal and non-fatal CVD endpoints were all reduced by statins and there was no clear evidence of any significant harm. However, the authors identified a risk of bias in many of the studies. Problems identified included: selective reporting of outcomes (particularly adverse effects); use of composite outcomes without reporting individual outcomes; stopping trials early (which may have overestimated the treatment effect) and the prominence of industry funding in all but one of the studies. This led the authors to conclude that caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk; in those with a 20% or higher risk of CVD over 10 years the likely benefits are greater than the harms.

PACEF Comment:
This Cochrane systematic review highlights the shortcomings of the published trials of statins for primary prevention of CVD. The authors conclude that the likely benefits of statins are greater than harms in people at high risk of cardiovascular events (>20% 10 year risk of CVD). This conclusion concurs with both local and NICE guidance that statins (simvastatin 40mg, or where this is inappropriate simvastatin 20mg or pravastatin 40mg) should be considered as part of a management strategy for primary prevention in people assessed as having a 10 year risk of CVD of 20% or higher.

Reference:
Taylor F et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2011, issue 1. Art. No.:CD004816. DOI:10.1002/14651858.CD004816.pub4

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE (*FEBRUARY 2011)

Daptomycin: risk of eosinophilic pneumonia

Daptomycin (Cubicin) is indicated for the treatment of complicated skin and soft-tissue infections and right sided infective endocarditis. It is administered by slow intravenous infusion and all treatment is managed within secondary/tertiary care. There have been rare but potentially serious reports of eosinophilic pneumonia associated with daptomyin.

The MHRA have issued the following advice to healthcare professionals

- The most common symptoms of eosinophilic pneumonia include cough, fever and dyspnoea. Most cases have occurred after 2 weeks of treatment.
- Healthcare professionals should react promptly to signs of eosinophilic pneumonia with daptomycin treatment. Daptomycin should be discontinued immediately and the patient treated with corticosteroids if appropriate.
- Daptomycin should not be re-administered to patients who have previously experienced eosinophilic pneumonia with this drug.
- All healthcare professionals are reminded to report all suspected adverse reactions with daptomycin through the Yellow Card Scheme.

Lenalidomide: risk of thrombosis and thromboembolism

Lenalidomide is authorised to be used in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one previous treatment. Multiple myeloma is known to be an independent risk factor for thromboembolic complications. Evidence from clinical trials and case reports suggests that lenalidomide may further increase the elevated risk of both venous and arterial thromboembolic reactions, including myocardial infarction and cerebrovascular accident in patients with myeloma.

The MHRA have issued the following advice to healthcare professionals:

- Patients receiving lenalidomide for the management of multiple myeloma should be closely monitored for evidence of arterial and venous thromboembolic events.
- Modifiable risk factors for thromboembolic events should be managed wherever possible (e.g. smoking cessation, control of hypertension and hyperlipdaemia).
- Medicines that increase risk of thromboembolism, such as oestrogens and erythropoietic agents should be used with caution during lenalidomide treatment.
- Appropriate thrombotic prophylaxis medication should be considered during lenalidomide treatment, particularly if patients with multiple risk factors, after careful assessment of the balance of risks and benefits in individual patients.
- Treatment with lenalidomide must be discontinued and anticoagulant therapy started in patients who experience thrombotic events. Once the patient has been stabilised on anticoagulant treatment and any complications of the thromboembolic event has been managed, lenalidomide may be restarted at the original dose after the reassessment of risks and benefits of treatment. Anticoagulation should then be continued throughout the course of lenalidomide treatment.

Omalizumab: potential risk of arterial thrombotic events

Omalizumab is a monoclonal antibody which inhibits immunoglobulin E and is licensed for the treatment of severe persistent allergic asthma in patients in whom standard treatment has failed. It is administered subcutaneously every 2-4 weeks. In controlled clinical trials and in an unpublished ongoing observational study (EXCELS) there was a higher incidence of arterial thrombotic events observed with omalizumab although this difference was not considered to be statistically significant at the 95% confidence interval. The MHRA have reminded all prescribers to be vigilant for possible thrombotic adverse reactions. All suspected adverse reactions, including arterial thrombotic events should be reported via the Yellow Card Scheme.

Dianeal, Extraneal and Nutrineal peritoneal dialysis solutions: risk of aseptic peritonitis due to presence of endotoxin

In December 2010 the potential for raised endotoxin levels was identified in 3 brands of peritoneal dialysis solutions (Dianeal, Extraneal and Nutrineal) manufactured by Baxter. Available evidence suggests that only a small proportion of solutions manufactured in Castlebar Ireland are likely to be affected however it is not possible to identify all potentially affected products. The presence of endotoxins increases the risk of aseptic peritonitis.

The MHRA have issued the following advice to healthcare professionals:

- Prioritise new unaffected PD solutions over solutions produced in Ireland especially for the vulnerable patients who critically depend on PD solutions. (including those receiving Extraneal with otherwise uncontrollable fluid overload, those with cardiac insufficiency and those with difficult to control diabetes).
- Consider other treatment options for other patients.
- Start new patients who require PD on products known not to be affected (e.g. non Baxter products or imported products not manufactured in Ireland).
- Be alert to the symptoms of aseptic peritonitis: cloudy effluent indicating an increased white cell count, abdominal pain, nausea, vomiting, fever and negative microbiological culture.
- Report any suspected reactions with all PD solutions to Baxter immediately using the adverse event reporting form specifying the batch number of product used. Reports are critically important to the rapid identification of affected batches.

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