NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 1 **January/ February 2010**

HAPPY NEW YEAR TO ALL OUR READERS

What's new this month:

- **The marketing authorisation for sibutramine (Reductil) has been suspended (see page 2).**
- **The new post-coital contraceptive ulipristal (Ellaone) is reviewed and designated GREEN for women presenting between 72 and 120 hours after unprotected intercourse or contraceptive failure (see page 3).**
- **A recent observational study identifies a decline in prescribing of chloramphenicol eye preparations for conjunctivitis compensated for by a rise in over-the-counter sales. We review the role of antibiotic eye preparations in the treatment of conjunctivitis (see page 4).**
- **After a recent meta-analysis finds an increased risk of falling in the over 60s associated with sedatives, hypnotics, antidepressants, antihypertensives and NSAIDs, we provide guidance on reviewing the medication of patients at risk (see page 6).**
- **New advice from the MHRA recommends that all ciclosporin should be prescribed and dispensed by brand name; nearly a third of Lincolnshire prescriptions for ciclosporin are written generically (see page 7).**
- **The NHS Bowel Cancer Screening Programme has been launched in Lincolnshire (see page 8).**

CONTENTS

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.lpct.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: DECEMBER 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Levonorgestrel 1500 microgram tablets (Levonelle 1500)	Post-coital contraception within 72 hours of unprotected intercourse as an emergency measure	GREEN NB Up to 72 hours after UPI or contraceptive failure, levonorgestrel (Levonelle 1500) is preferred first line.
Ulipristal 30mg tablets (Ellaone)	Emergency contraception within 120 hours (5 days) of unprotected intercourse or contraceptive failure.	GREEN NB Up to 72 hours after UPI or contraceptive failure, levonorgestrel (Levonelle 1500) is preferred first line. Ulipristal (Ellaone) should be preferred in patients presenting between 72 and 120 hours after UPI or contraceptive failure,
Topotecan 0.25mg and 1mg capsules (Hycamtin Oral)	As monotherapy for relapsed SCLC where retreatment with first line therapy is inappropriate	RED
Topotecan infusion (Hycamtin)	Relapsed small cell lung cancer (SCLC) where retreatment with first line therapy is inappropriate	RED-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 within licensed indications**. Specialist initiation and shared care guidelines are not considered necessary.

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.**

SUSPENSION OF MARKETING AUTHORISATION OF SIBUTRAMINE (REDUCTIL)

The European Medicines Agency (EMA) has recently completed a review of the Sibutramine Cardiovascular Outcomes Study (SCOUT) and has found that the cardiovascular risks of sibutramine outweigh the benefits. The SCOUT study was a randomised, double-blind, placebo controlled study involving approximately 10,000 obese and overweight patients with cardiovascular disease and/or type 2 diabetes mellitus over a six year period. Over this period, patients taking sibutramine experienced a 16% increased risk of cardiovascular events (e.g. myocardial infarction, stroke) compared to placebo. Juxtaposed with the relatively modest weight loss figures achieved using sibutramine in trials, the EMAs Committee for Medicinal Products for Human Use (CHMP) has concluded that these risks outweigh the

benefits. As a result of this, the marketing authorisation has been suspended across the European Union.

Advice for healthcare professionals and patients is as follows:

- Doctors should not issue any new prescriptions for sibutramine and should review all patients currently taking this medicine.
- Pharmacists should not dispense any prescriptions for sibutramine and should advise patients to make an appointment to discuss this with their doctor at the next convenient time.
- Patients currently taking sibutramine should make an appointment at the next convenient time to discuss alternative approaches to weight loss with their doctor. Patients may stop treatment before their appointment if they wish.

NEW DRUG ASSESSMENT: ULIPRISTAL 30MG TABLETS (ELLAONE)

Ulipristal (Ellaone) is the first oral emergency contraceptive licensed for use up to 120 hours (five days) after unprotected intercourse (UPI) or contraceptive failure. It is a progesterone receptor modulator and acts by delaying ovulation and follicular development. The alternative oral emergency contraceptive, levonorgestrel 1500 microgram (Levonelle 1500), should be taken as soon as possible after UPI, preferably within 12 hours and definitely within 72 hours. The only other option for women requiring emergency contraception between 72 hours and 120 hours (3 to 5 days) post UPI is to have an intra-uterine device (IUD) fitted. This is an invasive procedure that can only be undertaken by an appropriately trained healthcare professional.

Clinical evidence for ulipristal comes from four trials, only one of which has been fully published. The published trial compares the 50mg dose of ulipristal against levonorgestrel in the period 0 to 72 hours following UPI. This is not the current licensed dose of ulipristal, nor does it reflect the drug's full licensed indication. Results from this trial show that ulipristal has equivalent contraceptive efficacy to levonorgestrel in the period up to 72 hours following UPI. Further unpublished trials have also shown that ulipristal reduces the number of expected pregnancies if administered between the periods 72 to120 hours post UPI. There are currently no studies comparing the efficacy of ulipristal against the only other licensed alternative in the period 72 hours to 120 hours post UPI, the IUD.
The phase 2 trials used a 50mg capsule of ulipristal rather than the 30mg micronized form that has been brought to market as Ellaone. The Committee for Human Medicinal Products (CMHP) have confirmed that plasma levels reached with the 30mg micronized tablet formulation are approximately equivalent to those reached with the 50mg standard formulation used in trials. On this basis, PACEF have made the assumption that results obtained from trials where the 50mg dose was used, can be extrapolated to apply to the 30mg micronized formulation.

Side effects recorded with ulipristal are similar to those seen with levonorgestrel (Levonelle): nausea, vomiting, abdominal pain and disruption to the subsequent menstrual cycle.

Existing arrangements for post-coital emergency contraception centre on the provision of levonorgestrel (Levonelle) either on prescription or supplied direct from family planning clinics or community pharmacies according to a patient group direction. An over the counter preparation known as Levonelle One Step can also be purchased from community pharmacies.

Ulipristal is significantly higher in price than levonorgestrel (see cost comparison below):

Drug	Daily dose range	Cost (£)pa
Ulipristal 30mg tablets (Ellaone)	**30mg**	**£16.95**
Levonorgestrel (Levonelle 1500)	1500mcg	£5.37
Copper Intrauterine devices	Insert device, replace after 5 years	£8.00-13.08 per device

PACEF Recommendation:
PACEF were concerned by the relative paucity of published trial data and the need to extrapolate the results of studies using the 50mg ulipristal dose to the 30mg micronized formulation. Nonetheless, ulipristal is licensed for up to 120 hours (five days) after unprotected intercourse (UPI) or contraceptive failure and presents a preferable alternative to unlicensed levonorgestrel use or the use of an intrauterine contraceptive device (IUD). As a result of this ulipristal (Ellaone) is designated GREEN in patients presenting for emergency oral contraception between 72 and 120 hours after UPI or contraceptive failure. Patients presenting before 72 hours should continue to receive levonorgestrel 1500mcg (Levonelle 1500) either on prescription or through family planning clinics or community pharmacies.

KEY PATENT EXPIRIES 2010

The following table summarizes key patent expiries due to take place in 2010:

Date of Patent Expiry	Drug
January 2010	Lercanidipine
February 2010	Desloratidine
March 2010	Losartan
October 2010	Anastrazole
November 2010	Mizolastine
December 2010	Risedronate sodium

PACEF Comment:
PACEF will be undertaking a full review of prescribing for hay fever, including generic desloratidine, early in 2010. The potential impact of the losartan (Cozaar) patent expiry will also be considered in the spring as part of a more wide ranging review of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blocking Drugs.

NEW TRIALS IN BRIEF

Prescribing and over-the-counter sale of chloramphenicol eye preparations for conjunctivitis

In 2005, the Medicines and Healthcare products Regulatory Agency (MHRA) allowed, for the first time, over-the-counter sales of chloramphenicol ophthalmic preparations for acute bacterial conjunctivitis. At around the same time, three trials were published showing that antibiotic treatment of conjunctivitis had little clinical benefit in most patients. This observational study, using data from both the Prescription Pricing Division (PPD) and IMS data as well as data derived from an audit in four Oxford general practices reported that, including OTC sales, there was an overall increase in the use of chloramphenicol preparations of 47.8% over the

three year period from 2005 to 2007, despite a 15.5% decline in dispensed prescriptions[1].

PACEF Comment:
In one of the randomised controlled trials from 2005 referred to above, it was demonstrated that in children aged 6 months to 12 years with conjunctivitis, 80 to 85% had recovered after seven days whether or not they received antibiotic eye drops; about 15 to 20% still had symptoms after a week, even if they used antibiotic eye drops[2]. A similar pattern was identified in adults in a Cochrane Systematic Review published in 2006[3]. From this we can conclude that, for most people, topical antibiotic eye preparations will make little or no difference to recovery. For mild infections, no treatment remains the preferred option; bathing eyes with cool clean water is the recommended alternative. Many infections will clear within 2 to 5 days even without treatment. Delayed or post-dated prescriptions are an option for prescribers wishing to cover all eventualities. If symptoms persist or get worse or if presenting symptoms are severe, treatment is indicated; a medical opinion may need to be sought. Where treatment is considered necessary, the Health Protection Agency (HPA) recommend: chloramphenicol 0.5% eye drops 2 hourly reducing to four times a day plus chloramphenicol eye ointment 1% at night. Alternatively fusidic acid 1% gel twice daily is advocated. Treatment should continue for 48 hours beyond the resolution of symptoms

References
1. Davis H et al. Relative impact of clinical evidence and the over the counter prescribing on topical antibiotic use for acute infective conjunctivitis. *Br J Gen Pract* 2009; 59: 897-900.
2. Rose PW, et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet* 2005; 366: 37-43.
3. Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2006, Issue 2.

Medicines and falls

This is a meta-analysis of studies published between 1996 and 2007 in patients older than 60 which looked at the association between medication use and falls. The use of sedatives, hypnotics, antidepressants and benzodiazepines all demonstrated a significant association with falls with an increased relative risk of falling of around 50 to 70%. Antihypertensives and non-steroidal anti-inflammatory drugs (NSAIDs) may also be associated with a smaller, but significant risk of falling.

PACEF Comment:
Standard advice on reviewing medicines in those at risk of falling is featured as an appendix to this *Bulletin.*

Reference
Woolcott JC et al. Meta-analysis of the impact of 9 medication classes on falls in elderly people. *Arch Intern Med* 2009; 169(21): 1952 – 1960.

Long-Acting Beta-2 Agonist (LABA) and Inhaled Corticosteroid (ICS) combination therapy in asthma

This is a systematic review that evaluates the clinical effectiveness, safety and cost-effectiveness of LABA-ICS combination therapy in adults (12 years of age or older) diagnosed with persistent asthma. The review concludes that there are statistically important but not clinically meaningful benefits from LABA-ICS treatment compared with ICS treatment alone and that, for most patients with persistent asthma, the only

maintenance therapy that is required is an ICS. The economic evaluation suggests that the introduction of a LABA before patients have tried high dose ICS monotherapy may not be justified. No clinically significant differences between currently available LABA-ICS combination inhalers were found.

Reference
Canadian Agency for Drugs and Technologies in Health, Technology Report: Long-Acting Beta-2 Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation. HTA, Issue 122 November 2009

NICE TECHNOLOGY APPRAISAL 184: *TOPOTECAN FOR THE TREATMENT OF RELAPSED SMALL-CELL LUNG CANCER* (NOVEMBER 2009)

Key points are as follows:

Oral topotecan is recommended as an option only for people with relapsed small-cell lung cancer to whom:-

- re-treatment with the first-line regimen is not considered appropriate **and**
- the combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated.

Intravenous topotecan is not recommended for people with relapsed small-cell lung cancer.

PACEF Recommendation:
Topotecan capsules (Hycamtin Oral) are designated RED within licensed indications (i.e. as monotherapy for patients with relapsed small-cell lung cancer where re-treatment with the first-line therapy is not considered appropriate). Intravenous topotecan (Hycamtin) is designated RED-RED for the same indication.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (DECEMBER 2009)

Ciclosporin must be prescribed and dispensed by brand name

- Ciclosporin is a critical dose drug with a narrow therapeutic index
- Patients should be stabilised on a single brand of ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in bioavailability.
- Prescribing and dispensing of ciclosporin should be by brand name.
- When switching a patient stabilised on one brand of ciclosporin onto another brand is unavoidable, the patient should be closely monitored for side effects, drug blood concentrations and transplant function.

PACEF Recommendation:
Steps should be taken to ensure that the same brand of ciclosporin is always prescribed and dispensed to the patient. All prescribing of ciclosporin should be by brand name to minimise potential confusion. At present in Lincolnshire only 69% of ciclosporin prescriptions are prescribed by brand.

Potential risk of male breast cancer with finasteride

- Cases of male breast cancer have been reported with finasteride (Proscar and Propecia).
- Patients should be advised to promptly report to their doctor any changes in their breast tissue such as lumps, pain or nipple discharge.

MEDICINES, SIDE EFFECTS AND THE RISK OF FALLS IN THE ELDERLY: AN AID TO MEDICATION REVIEW

Often a combination of medicines can contribute to an increased risk of falling (e.g. dehydration from inadequate fluid intake and a loop diuretic, postural hypotension from an antihypertensive and sedation from a benzodiazepine). The risks and benefits of each medicine should be considered when deciding which medicines to stop or reduce.

Central nervous system (CNS)

- Elderly patients are more susceptible to the CNS side effects of drugs, leading to excessive sedation, increased body sway and slowing of reaction time.
- Drugs with anticholinergic properties may lead to confusion and "mental fuzziness" in the elderly.

Nitrazepam, diazepam, temazepam, zopiclone	*See BNF for guidance on benzodiazepine withdrawal*
Amitriptyline, dosulepin (dothiepin), imipramine, trazadone	*Slowly withdraw tricyclics or change to SSRI*
Haloperidol, chlorpromazine, risperidone	*Use lowest possible doses*
Barbiturates, chlorpheniramine, hydroxyzine, cyclizine, benzhexol, procyclidine, oxybutynin, tolterodine	. *Check medication is still indicated*

Hypotension

Orthostatic blood pressure control (control of blood pressure at rest and movement) is already impaired in the elderly, so they are more likely to suffer drug-induced postural hypotension, which can lead to dizziness and falls.

Furosemide, bendroflumethiazide. atenolol, bisoprolol, propranolol, timolol eye drops. captopril, lisinopril, enalapril, ramipril, doxazosin, prazosin. nifedipine, diltiazem, amlodipine, verapamil. hydralazine, nitrates.	*Check standing and sitting BP. If postural BP drop >20mmHg treat to standing BP. The dose of some antihypertensives may need to be reduced as the patient ages.* *Consider risk from falling vs risk from hypertension.* *Consider home monitoring of BP to exclude "white coat" hypertension.*
Haloperidol, chlorpromazine, risperidone. amitriptyline, dosulepin (dothiepin), imipramine, trazodone, citalopram, paroxetine, fluoxetine, Prochlorperazine. Morphine, codeine, dihydrocodeine.	*Check standing and sitting BP.* *Check medication still indicated.* *Use SSRI if antidepressant indicated.* *Use paracetamol instead of co-analgesics.* *Use lowest dose of opiate where indicated.*
Levodopa preparations, dopamine agonists such as bromocriptine, pergolide, cabergoline	*Use lowest effective doses*

Dehydration **The patient's general health influences what effects a medicine might have. Dehydration can make postural hypotension more likely**.	
Lactulose, docusate, senna, bisacodyl	*Excessive use of laxatives can lead to dehydration. Ispaghula husk may be preferable.*
Alcohol, inadequate fluid intake	*Ensure adequate fluid intake (8 cups of water per day)*
Effervescent analgesics (high sodium content)	*Use capsules, easy swallow tablets or liquid instead*

Other Potential Causes of falls in the elderly	
Digoxin	*Digoxin toxicity may cause confusion. Measure plasma level if suspected.*
Baclofen, dantrolene	*Muscle Spasticity. Titrate dose*
Carbamazepine, phenytoin	*Ataxia if dose too high – measure plasma levels*
Prochlorperazine, metoclopramide	*Can cause drug induced Parkinson's disease, avoid if possible*
Procyclidine, benzhexol	*Avoid or minimise use if possible.*

THE NHS BOWEL CANCER SCREENING PROGRAMME

Bowel cancer is the third most common cancer in the UK; one in twenty people will develop the disease sometime during their lifetime. It kills approximately 16,000 people a year with more than 80% of cases diagnosed in people over the age of 60.

The NHS Bowel Cancer Screening Programme was launched in Lincolnshire at the end of December 2009. The Regional Hub, based at Queen's Medical Centre in Nottingham, will send Faecal Occult Blood test (FOBt) kits to men and women aged 60 to 69 years who are registered with the NHS. 1000 invitations for bowel screening will be sent out each week by the Hub. After two years the target age range will be widened to include those aged 70 to 75.
People will be asked to return the kits to the Hub for processing. Those people identified as having an abnormal result will be offered an appointment with a specialist screening practitioner (SSP – a nurse working within the programme). Weekly clinics will be held at Lincoln, Pilgrim and Grantham Hospitals to cover these appointments.

At the SSP appointment, patients will be assessed and offered colonoscopy, (dependent upon fitness): this will be performed at Lincoln County Hospital. If no abnormality is detected, the patient will be re-entered onto the screening programme and will receive a further FOBt in 2 years. Patients found to have bowel cancer will be referred to their local Colorectal Cancer Multidisciplinary Team and a treatment programme will be decided upon.

It is not envisaged that this screening programme will generate a great deal of extra work for GPs. The patient's GP will be kept informed of findings at all stages; if a referral is required for any other benign colonic condition this will be highlighted.
A more detailed information pack has been produced and circulated to practices.

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