NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 14 **September 2010**

What's new this month:

- **Low strength bimatoprost 0.01% eye drops (Lumigan) have not been approved for use (see page 3).**
- **Further evidence supports a link between proton pump inhibitor use and an increased risk of *Clostridium difficile* infection (see page 6).**
- **Orciprenaline syrup (Alupent) is finally withdrawn (see page 9).**
- **The NPSA have issued a Rapid Response Report designed to reduce the risk of patient safety incidents linked to the wrong dose of insulin being prescribed, dispensed or administered (see page 9).**

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

SUMMARY OF PACEF DECISIONS: JULY 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Adalimumab (Humira) injection	Licensed for severe, active Crohn's disease in people whose disease has not responded despite full and adequate treatment with an immunosuppressant and/or corticosteroid, or who are intolerant to or have contraindications to such therapies.	RED subject to NICE criteria for initiation, monitoring and discontinuation.
Bimatoprost 0.1mg per ml drops (Lumigan) (0.01%) (3ml bottle)	As monotherapy or as an adjunct to beta-blockers (BBs) in chronic open angle glaucoma (COAG) or ocular hypertension (OHT)	RED-RED

Bimatoprost 0.3mg per ml drops (Lumigan) (0.03%) (3ml bottle)	As monotherapy or as an adjunct to beta-blockers (BBs) in chronic open angle glaucoma (COAG) or ocular hypertension (OHT)	AMBER
Infliximab (Remicade) infusion	Licensed for: (1) severe, active Crohn's disease in people whose disease has not responded despite a full and adequate course of therapy with corticosteroid and/or an immunosuppressant, or who are intolerant to or have medical contra-indications for such therapies. (2) fistulising, active Crohn's disease in people whose disease has not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). (3) severe, active Crohn's disease in people aged 6 to 17 years whose disease has not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy, or who are intolerant to or have contraindications for such therapies.	RED subject to NICE criteria for initiation, monitoring and discontinuation.
Orciprenaline syrup 10mg in 5ml (Alupent)	Licensed for reversible airways obstruction	RED-RED
Pemetrexed (Alimta) injection	Licensed for use with cisplatin for the first line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology and as monotherapy for second line treatment.	RED subject to NICE criteria
Somatropin injection (Genotropin, Humatrope, Norditropin, NutropinAq, Omnitrope, Saizen and Zomacton)	The licensed indications of commercially available somatropin formulations are as follows: • growth disturbance in children due to insufficient secretion of growth hormone (growth hormone deficiency) • growth failure in girls associated with gonadal dysgenesis (Turner syndrome). • growth retardation in prepubertal children associated with chronic renal insufficiency. • improvement of growth and body composition in children with Prader-Willi syndrome. • growth disturbance in short children born small for gestational age, with a birth weight and/or length below -2SD, who fail to show catch-up growth by 4 years of age or later. • growth failure associated with SHOX deficiency, as confirmed by DNA analysis.	AMBER subject to shared care guidelines and NICE criteria for initiation, monitoring and discontinuation.
Sorafenib (Nexavar) tablets	Licensed for the treatment of hepatocellular carcinoma.	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.**

RAPID DRUG ASSESSMENT: BIMATOPROST 0.01% EYE DROPS (LUMIGAN)

Bimatoprost 0.01% eye drops (Lumigan) is a new low strength formulation of an already existing product. It is licensed for the reduction of elevated intraocular pressure in chronic open-angle glaucoma (COAG) and ocular hypertension (OHT) in adults (as monotherapy or as adjunctive therapy to beta-blockers). Bimatoprost is a prostamide analogue and works by increasing uveoscleral outflow resulting in reductions of intra-ocular pressure (IOP) of between 25 and 35%. The 0.03% strength has previously been reviewed by PACEF and designated AMBER (see *PACE Bulletin* Vol 4 No 6 (May 2010)).

Bimatoprost 0.01% eye drops have been launched with claims that they are as effective as bimatoprost 0.03%, but with fewer adverse effects, in particular hyperaemia. PACEF reviewed a single prospective, randomised, double-blind, multicentre trial. Patients with COAG or OHT were randomised to receive either bimatoprost 0.01% (n=186), bimatoprost 0.0125% (n=188) or bimatoprost 0.03% (n=187) once daily in the evening for 12 months. The primary efficacy measure was change to intraocular pressure (IOP). In addition, adverse events were also monitored and recorded and an objective assessment of conjunctival hyperaemia undertaken.

The study concluded that bimatoprost 0.01%, but not bimatoprost 0.0125%, was equivalent in efficacy to bimatoprost 0.03% in terms of reduction in IOP. The percentage of patients with a moderate to severe increase from the baseline macroscopic hyperaemia score was higher in the bimatoprost 0.0125% and 0.03% groups (9.0% and 9.1% respectively) than the bimatoprost 0.01% group (3.2%). The overall incidence of treatment-related adverse events was reduced significantly in the bimatoprost 0.01% and 0.0125% groups compared with the bimatoprost 0.03% group (38.4% and 39.9% vs 50.8%).

A cost comparison between the two strengths reveals the following:

	Cost (3ml bottle)
Bimatoprost 0.1mg per ml drops (Lumigan) (0.01%)	£12.43
Bimatoprost 0.3mg per ml drops (Lumigan) (0.03%)	£10.30

Prices taken from *MIMS* August 2010

The financial impact on Lincolnshire primary care of all 0.03% bimatoprost prescribing transferring over to the new 0.01% product would be £47,610pa.

PACEF Recommendation

PACEF were concerned that bimatoprost 0.0125% was not found to be equivalent in efficacy to bimatoprost 0.03% in the trial reviewed. This seemed to cast doubt on the quality of the study results and to potentially challenge the conclusion that bimatoprost 0.01% is equivalent in efficacy to bimatoprost 0.03% in terms of reduction in IOP. Further studies are necessary to clarify these findings. On the basis of this uncertainty, PACEF were unable to justify a move to this lower strength, higher cost formulation at this stage. As a result of this, bimatoprost 0.1mg per ml drops (Lumigan) (0.01%) are designated RED-RED; bimatoprost 0.3mg per ml drops (Lumigan) (0.03%) remain AMBER.

Reference

Katz L.J ., 'Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension'. *Ophthalmol* 2010; 149: 661-671.

NICE TECHNOLOGY APPRAISAL 187: INFLIXIMAB (REVIEW) AND ADALIMUMAB FOR THE TREATMENT OF CROHN'S DISEASE (MAY 2010)

The key recommendations are as follows:

- **Infliximab and adalimumab**, within their licensed indications, are recommended as treatment options for **adults with severe active Crohn's disease** whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.
- Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate.
- **Infliximab**, within its licensed indication, is also recommended as a treatment option for people with **active fistulising Crohn's disease** whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy.
- Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate.
- Treatment with infliximab or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.
- Infliximab, within its licensed indication, is recommended for the treatment of **people aged 6–17 years with severe active Crohn's disease** whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or

have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.

- Severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above.
- **Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease.**

PACEF Recommendation
Infliximab (Remicade) intravenous infusion is approved for severe active Crohn's disease (both in adults and children aged 6 to 17) and active fistulising Crohn's disease within licensed indications and subject to NICE initiation, monitoring and discontinuation criteria. Designation: RED.
Adalimumab (Humira) injection is approved for severe active Crohn's disease in adults within licensed indications and subject to NICE initiation, monitoring and discontinuation criteria. Designation: RED.

NICE TECHNOLOGY APPRAISAL 188: *HUMAN GROWTH HORMONE (SOMATROPIN) FOR THE TREATMENT OF GROWTH FAILURE IN CHILDREN* (MAY 2010)

The key recommendations are as follows:

Somatropin (recombinant human growth hormone) is recommended as a treatment option for children with growth failure associated with any of the following conditions:

- **growth hormone deficiency**
- **Turner syndrome**
- **Prader–Willi syndrome**
- **chronic renal insufficiency**
- **born small for gestational age with subsequent growth failure at 4 years of age or later**
- **short stature homeobox-containing gene (SHOX) deficiency.**

Treatment with somatropin should always be initiated and monitored by a paediatrician with specialist expertise in managing growth hormone disorders in children.

Treatment with somatropin should be discontinued if any of the following apply:

- growth velocity increases less than 50% from baseline in the first year of treatment
- final height is approached and growth velocity is less than 2 cm total growth in 1 year
- there are insurmountable problems with adherence
- final height is attained.

Treatment should not be discontinued by default. The decision to stop treatment should be made in consultation with the patient and/or carers either by: a paediatrician with specialist expertise in managing growth hormone disorders in

children, or an adult endocrinologist, if care of the patient has been transferred from paediatric to adult services.

PACEF Recommendation
Somatropin is currently an AMBER drug and is approved for shared care within licensed indications and NICE criteria subject to shared care guidelines. A range of products are available in the UK including: Genotropin, Humatrope, Norditropin, NutropinAq, Omnitrope, Saizen and Zomacton.

NICE TECHNOLOGY APPRAISAL 189: *SORAFENIB FOR THE TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA* (MAY 2010)

The key recommendations are as follows:

Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are not suitable.

PACEF Recommendation:
Sorafenib (Nexavar) tablets are not recommended for the treatment of advanced hepatocellular carcinoma. Designation: RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL GUIDELINES 190: *PEMETREXED FOR THE MAINTENANCE TREATMENT OF NON-SMALL-CELL LUNG CANCER* (JUNE 2010)

The key recommendations are as follows:

- People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment.
- Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

PACEF Recommendation
Within licensed indications and NICE initiation criteria, pemetrexed (Alimta) injection is designated RED.

NEW TRIALS IN BRIEF

Proton Pump Inhibitors (PPIs) and the risk of *Clostridium difficile* infection

Two studies this month potentially add weight to a possible link between PPIs and Clostridium difficile. A large observational study conducted in a hospital in the United States (101,796 admissions, 665 cases of *C. difficile* infection over a 5 year period) suggests that inpatients taking daily PPIs were 70% more likely to develop *C. difficile* infection than non-users. A separate retrospective cohort study used databases in a US hospital to investigate recurrence rates of *C difficile* associated with PPI use. Recurrence rates of *C difficile* infection (15 – 90 days after the initial infection) were compared in 527 patients prescribed PPIs within 14 days after *C difficile* infection

compared with 639 patients who were not prescribed PPIs within this period. Patients on PPIs were 40% more likely to experience a recurrence of the infection.

PACEF comment:
These studies add weight to existing concerns about a possible link between regular PPI use and *C. difficile* infection. Standard advice is to review current treatment where *C. difficile* infection is suspected. If the patient is taking an antibiotic or a PPI, these drugs should be discontinued, where possible.

References
Howell M.D. et al., Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Int Med* 2010; 170(9): 784 – 790
Linsky A et al., Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Int Med* 2010; 170(9): 772 – 778

Antibiotic resistance

This is a systematic review of the literature on the prescribing of antibiotics in primary care and subsequent antibiotic resistance in individuals. In 5 studies of urinary tract bacteria, the pooled odds ratio (OR) for resistance was 2.5 within 2 months of antibiotic treatment and 1.33 within 12 months. In 7 studies of respiratory tract bacteria, pooled ORs were 2.4 and 2.4 for the same periods respectively. Longer duration and multiple courses of antibiotics were associated with higher levels of resistance.

PACEF comment:
This systematic review provides important primary care based evidence confirming that commonly used antibiotics for respiratory tract and urinary tract infections impact on bacterial resistance in an individual that persists for 12 months. The greater the number or duration of antibiotic courses prescribed the greater the likelihood that resistant bacteria would be isolated from the patient. This further justifies existing messages around avoiding inappropriate antibiotic use.

Reference
Costelloe C et al., Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; 340: c2096.

Side effects and unintended benefits of statin therapy

This is a large UK prospective cohort study of the unintended effects of statins undertaken using the QResearch (GP) database. A cohort of 226,000 patients who were new users of statins between 2002 and 2008 was identified from a population of 2 million patients. Statin use was associated with decreased risks of oesophageal cancer, but increased risk of liver dysfunction, acute renal failure, myopathy and cataract. A dose response relationship was found for acute renal failure and liver dysfunction. Adverse effects were similar across statin types except liver dysfunction where risks were highest for fluvastatin. There was no increased risk of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, fracture and several cancers**. For every 10,000 women with a >20% CV risk treated with statins for 5 years, 271 cases of cardiovascular disease would be prevented, 8 fewer cases of oesophageal cancer would be identified and there would be 23 extra patients with acute renal failure, 73 extra patients with liver dysfunction, 307 extra patients with cataracts and 39 extra patients with muscle weakness. Figures were similar for men, except that there would be 110 extra cases of muscle weakness.**

PACEF comment:
This study confirms the side effects of statins and provides some further information on unintended benefits. It provides useful Number Needed to Treat (NNT) and Number Needed to Harm (NNH) figures on key adverse effects and helps to quantify concerns over statin related myopathy and liver dysfunction. Further discussion of statin related myopathy appeared in *PACE Bulletin* Vol 4 No 13 (August 2010).

Reference:
Hippisley-Cox J et al. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010; 340: c2197

Angiotensin 2 receptor antagonists (A2RAs) and cancer risk

A meta-analysis of 9 RCTs has examined the effect of A2RAs on the occurrence of new cancers. Patients randomly assigned to A2RAs had a significantly increased risk of new cancer occurrence compared to the control group (7.2% vs. 6%). No significant excess in cancer mortality was found.

PACEF comment:
This study shows an association between A2RAs and a very modest increase in cancer risk, but does not prove that A2RAs cause cancer. Regulators have announced that they will be reviewing this meta-analysis and other data. In the meantime ACE inhibitors should remain the first-line choice when a renin-angiotensin system drug is indicated.

Reference
Sipahi I et al., Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *The Lancet Oncology*, early online publication, 14 June 2010 doi:10.1016/S1470 -2045(10)70106-6

Non-Steroidal Anti-Inflammatory Drugs and cardiovascular risk

A large Danish observational study has assessed the cardiovascular (CV) safety of five NSAIDs in over 1 million healthy individuals aged over 9 yrs. Over a 9 year period, use of NSAIDs within 30 days of a CV event was tracked. The results of the study suggest that even in healthy individuals, short term use of diclofenac (and rofecoxib) appears to be associated with CV risk. Naproxen appeared to have the lowest CV risk. The risk of serious bleeding was similar for naproxen and diclofenac, although the confidence intervals were wide for naproxen.

PACEF Comment:
This large, well conducted study has limitations, but supports the findings of RCTs and other observational studies: diclofenac appears to have a higher thrombotic risk than other non-coxib NSAIDs, particularly naproxen. This study re-emphasises that, even in healthy individuals, diclofenac appears to be associated with increased CV risk which may be similar to rofecoxib; naproxen appears to be associated with lower CV risk. This is of concern on a population basis because diclofenac remains the most commonly prescribed NSAID both nationally and locally, still accounting for about 38% of all NSAID prescriptions in Lincolnshire. Prescribers are urged to continue to review existing diclofenac prescribing and to reduce new initiations.

Reference
Fosbol EL et al., Cause-specific cardiovascular risk associated with non-steroidal anti-inflammatory drugs among healthy individuals. *Circ Cardiovasc Qual Outcomes* published on-line.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (JULY 2010)

Orciprenaline sulphate (Alupent) reminder of withdrawal from the market on September 30th 2010

Readers of the *PACE Bulletin* will already be aware of the planned withdrawal of orciprenaline syrup 10mg in 5ml (Alupent). This is due to an association with a significantly increased incidence of cardiac side effects, mainly palpitations and tachycardia, compared to similar products. The MHRA have previously advised that patients who require a liquid oral formulation of a beta-agonist should be switched to a more selective short-acting beta2-agonist such as salbutamol or terbutaline. In the July *Drug Safety Update* the MHRA remind all prescribers of the planned withdrawal of this product and advise that all patients must be transferred to alternative bronchodilator therapy as soon as possible.

PACEF Recommendation
All remaining patients receiving prescriptions for orciprenaline syrup 10mg in 5ml (Alupent) should be reviewed and transferred to an alternative preparation.

NATIONAL PATIENT SAFETY AGENCY: RAPID RESPONSE REPORT – *SAFER ADMINISTRATION OF INSULIN* (JUNE 2010)

The National Patient Safety Agency (NPSA) has issued a Rapid Response Report in response to the high number of incidents reported resulting from the wrong dose of insulin being administered. Common causes of error with insulin are inaccurate dosing and/or administration resulting in either hyperglycaemia or hypoglycaemia.

Two common errors have been identified:

- **The inappropriate use of non-insulin (IV) syringes (marked in mls and not insulin units) for administration.**
- **The use of abbreviations such as 'U' or 'IU' for units. When abbreviations are added to the intended dose, the dose may be misread (e.g. 10U read as 100).**

The NPSA make a number of key recommendations that must be implemented by 16th December 2010:

(1) All regular and single insulin (bolus) doses must be measured and administered using an insulin syringe or commercial insulin pen device. Intravenous syringes must never be used for insulin administration.

Over 94% of the insulin prescribed in Lincolnshire is via commercial pen devices. There are a wide range of these devices available which differ in terms of maximum/minimum dose delivered and how they operate. One of the incidents outlined in the NPSA RRR involved the incorrect use of an Opticlick pen device by a community nurse. This resulted in the patient receiving ten times the required dose of insulin with fatal consequences. There is a general recommendation that all health care professionals who may be required to prepare and administer insulin from similar devices should ensure that they are sufficiently familiar with the product and have sufficient personal knowledge, skills and competence regarding the administration of insulin.

There are currently no insulin syringes available for the administration of insulin 500. The NPSA have stated that they are currently working with industry to develop 500 units per ml syringes, although no timescale has been confirmed.

(2) When prescribing and administering insulin, the term 'units' should be used in all contexts. Abbreviations, such as 'U' or 'IU' should no longer be used.

Prescribers, dispensers and pharmacists should take steps to ensure that old-style abbreviations for 'units' are no longer used on prescriptions or on dispensed labels. Local polices and procedures will need to be amended to include a statement requiring the use of units in full and warning of the risks of using abbreviations.

(3) All clinical areas and community staff treating patients with insulin will need to hold adequate supplies of insulin syringes and subcutaneous needles.

(4) Training should be available for all healthcare staff (including medical staff) expected to prescribe, prepare and administer insulin. An e-learning programme is available from: www.diabetes.nhs.uk/safe use of insulin

PACEF Recommendation:
Staff are urged to familiarise themselves with this RRR and to ensure that all key actions have been implemented by 16th December 2010.

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