NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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What's new this month?

- **Ketamine oral solution (50mg in 5ml) and injection have been approved for use in palliative care for the management of pain unresponsive to standard therapies. Designation AMBER subject to the development of shared care guidelines (see page 2).**
- **A new antihistamine, bilastine (Ilaxten), is designated RED-RED (see page 4).**
- **Linezolid (Zyvox) is designated RED; full courses should be prescribed and supplied from secondary/tertiary care (see page 4).**
- **Increasing concerns over the cardiovascular risk associated with the tiotropium Spiriva Respimat device are reported (see page 7).**
- **A new paracetamol dosing schedule for children has been launched (see page 9).**
- **The MHRA have now published their findings on pioglitazone and bladder cancer (see page 10).**

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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: JULY 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Bilastine 20mg tablets (Ilaxten)	Licensed for the symptomatic treatment of allergic rhino-conjunctivitis and urticaria.	RED-RED
Erlotinib tablets (Tarceva)	Licensed as monotherapy for maintenance treatment of locally advanced or metastatic non-small-cell lung cancer in patients with stable disease after platinum-based chemotherapy.	RED-RED
Golimumab injection (Simponi)	Licensed in combination with methtrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) when response to disease modifying anti-rheumatic drugs (DMARD) (including MTX) has been inadequate.	RED N.B. Golimumab injection is not approved for use in methotrexate naïve patients
Ketamine injection (Ketalar)	Unlicensed indication. For use either orally or subcutaneously in palliative care for the management of pain unresponsive to standard therapies	AMBER Shared Care Guideline in development
Ketamine oral solution 50mg in 5ml	Unlicensed. For use in palliative care for the management of pain unresponsive to standard therapies.	AMBER Shared Care Guideline in development
Linezolid 600mg tablets (Zyvox) Linezolid 100mg/5ml suspension (Zyvox)	Licensed for the treatment of community acquired pneumonia, nosocomial pneumonia, skin infections and soft tissue infections when the causative organism is known to be a Gram-positive bacteria.	RED
Rituximab infusion (MabThera)	Licensed for maintenance therapy in patients with relapsed or refractory follicular non-Hodgkin's lymphoma that has responded to induction therapy with chemotherapy (with or without rituximab)	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.**

NEW DRUG ASSESSMENT: *KETAMINE ORAL SOLUTION (50MG IN 5ML) AND KETAMINE INJECTION FOR PALLIATIVE CARE*

Ketamine is a dissociative anaesthetic with analgesic properties when used in sub-anaesthetic doses. It has been used in Lincolnshire for a number of years under

specialist supervision to manage complex pain refractory to other measures. In response to an increasing number of approaches to GPs asking them to prescribe ketamine, predominantly within the context of palliative care, PACEF undertook an assessment of the formulations involved. Ketamine is available either as an oral suspension 50mg/5ml or as an injection that can be administered orally or subcutaneously. Neither of these formulations are licensed for analgesic purposes.

The analgesic properties of ketamine have been thoroughly investigated and the analgesic dose range is well established. Ketamine has been used off-license in the acute hospital setting to provide intense analgesia for painful procedures (e.g. in Accident and Emergency or post surgery). Despite the lack of a licensed formulation, ketamine is recommended in both the current edition of the *Palliative Care Formulary* and the *Oxford Textbook of Palliative Medicine* for the management of pain unresponsive to standard therapies.

Overall the evidence base for ketamine as an analgesic in palliative care is comparatively weak due to the absence of large-scale published clinical trials. Most of the evidence reviewed by PACEF comes from retrospective studies, including individual case reports. In addition, ketamine is associated with a number of adverse effects, the most common being vivid dreams, hallucinations, excessive secretions and sedation. Rarer side effects include psychosis, hypertension and tachycardia. Adverse or unwanted side effects can be managed by the concurrent use of various other agents (e.g. midazolam, diazepam or haloperidol). Ketamine does not depress respiration but can potentiate the action of opioids necessitating a reduction in opioid dose.

Using oral solution, a month's treatment costs approximately £350. If the same dose is administered orally using the injection solution the cost is approximately £49.

Ketamine is only considered by the palliative care team for the management of pain which is not relieved by standard therapies (e.g. morphine and alternative adjuvant analgesics) and when there are limited alternative options available. In practice, this results in approximately 10 patients per year being initiated on ketamine for palliative care in Lincolnshire; of these, approximately 50% (5 patients) are potentially appropriate for home care.

PACEF Recommendation

Despite the weak evidence base and concern over adverse effects, PACEF recognise that ketamine is acknowledged by both local and national opinion leaders as having a role in palliative care for the management of pain unresponsive to standard therapies. As a result of this, ketamine oral solution 50mg in 5ml (unlicensed) and ketamine injection (unlicensed) are designated AMBER and are approved for GP prescribing for palliative care subject to the development of comprehensive shared care guidelines. Ketamine for this indication must only be initiated by the Lincolnshire Palliative Care Team based at St Barnabas Hospice. GP prescribing is only appropriate subject to specialist initiation and stabilisation and within the context of the SCG. The SCG is being developed as a matter of priority and should be available shortly. The publication of the SCG will be reported in a future *PACE Bulletin.* Ketamine oral solution/ injection remain under review for other types of pain (e.g. neuropathic pain) but have only been approved for palliative care.

RAPID DRUG ASSESSMENT: *BILASTINE 20MG TABLETS (ILAXTEN)*

Bilastine is a second generation H_1 receptor antagonist (or antihistamine) licensed for the symptomatic treatment of allergic rhino-conjunctivitis and urticaria. The main supporting evidence comes from a series of randomised placebo controlled, double blind clinical trials; in some of these trials bilastine is compared against an active comparator (e.g. cetirizine, fexofenadine and desloratadine). Results from the trials confirm that bilastine is an effective antihistamine equivalent in effect to the active comparators when used to reduce symptoms associated with allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

However, the majority of trials were of short duration (14-28 days) and provide no useful information on long-term safety or efficacy. Bilastine emerged from these trials as well tolerated in relation to the comparator antihistamines, but longer and larger trials are required to determine whether this is of any significance in longer-term therapy.

A cost comparison reveals that bilastine is approximately 15 times more expensive than standard first line non-sedating antihistamines:

	Daily dose	Cost (30 days)
Bilastine 20mg tablets (Ilaxten)	**20mg daily**	**£15.09**
Cetirizine 10mg tablets (generic)	10mg daily	£1.06
Loratadine 10mg tablets (generic)	10mg daily	£1.16
Desloratadine 5mg tablets (NeoClarityn)	5mg daily	£6.77
Fexofenadine 120mg tablets (generic)	120mg daily	£2.57
Levocetirizine 5mg tablets (Xyzal)	5mg daily	£4.39
Rupatadine 10mg	10mg daily	£5.00

PACEF Recommendation:
Bilastine (Ilaxten) emerges from short-term studies as comparable in effectiveness to cetirizine, fexofenadine and desloratadine. However, it is fifteen times the price of standard first line generic non-sedating antihistamines (cetirizine and loratadine) and three times the price of non-recommended branded stereoisomer products such as desloratadine and levocetirizine. Claims that it is better tolerated than alternatives cannot be substantiated from the short-term studies available. As a result of this, bilastine (Ilaxten) tablets 20mg are designated RED-RED.

RAPID DRUG ASSESSMENT: *LINEZOLID 6OOMG TABLETS AND 100MG/5ML ORAL SUSPENSION (ZYVOX)*

Linezolid (Zyvox) is an oxazolidinone antibacterial licensed for the treatment of community acquired pneumonia, nosocomial pneumonia, skin infections and soft tissue infections when the causative organism is known to be a Gram-positive bacteria. Specifically, linezolid is active against meticillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci; it has no activity against Gram-negative pathogens. The product license specifies that linezolid should only be initiated in a hospital environment and after consultation with a microbiologist or

infectious disease specialist. It is ULHT policy that linezolid can only be initiated on the recommendation of a microbiologist.

The recommended adult dose of linezolid is 600mg twice daily for between 10-14 days; the NHS cost of such a course is between £1,246 and £2,492.

Linezolid is associated with a high incidence of blood disorders (e.g. thrombo-cytopenia, anaemia, leucopoenia) and optic neuropathy with incidence increasing if use extends beyond 28 days. The prevalence of blood disorders is such that weekly full blood counts are recommended, particularly if the course length extends beyond 10-14 days. Close monitoring is advocated for all patients but especially those who:

- are receiving treatment for more than10-14 days.
- have pre-existing myelosuppression.
- are receiving drugs that may have adverse effects on haemoglobin, blood counts or platelet function.
- have severe renal impairment.

There is also a Commission on Human Medicines (CHM) warning on the risk of optic neuropathy associated with linezolid. The CHM recommend that patients should be warned to report symptoms of visual impairment including blurred vision, visual field defect, changes in visual acuity and colour vision. Patients experiencing new visual symptoms regardless of treatment length should be evaluated promptly and referred to an ophthalmologist if necessary. Visual function should be monitored regularly if treatment is longer than 28 days.

Linezolid use is also associated with a wide range of other adverse effects and, as a reversible non-selective monoamine oxidase inhibitor (MAOI), it has numerous food and drug interactions, especially with psychotropic medication.

PACEF Recommendation

PACEF have identified some GP prescribing of this product, sometimes in quantities that suggest a longer duration of therapy than 10 to 14 days. Linezolid 600mg tablets and granules for oral suspension 100mg in 5ml (Zyvox) are currently designated RED. They should only be initiated on the recommendation of a microbiologist with the full treatment course supplied from secondary care. GPs approached and asked to prescribe linezolid should refuse. Linezolid is a potentially toxic drug that requires close monitoring to minimise the risks associated in particular with extended therapy. Unsupported GP prescribing of linezolid in any context is strongly discouraged at this time. PACEF recognise that there may be exceptional circumstances in which longer-term linezolid on the recommendation of a microbiologist is justified and are working with ULH microbiologists to develop a shared care guideline for future consideration by ULH Drug and Therapeutics Committee and PACEF. In the interim period linezolid (Zyvox) remains a RED drug and should not be prescribed in primary care.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 224: *GOLIMUMAB FOR THE TREATMENT OF METHOTREXATE-NAÏVE RHEUMATOID ARTHRITIS* (TERMINATED APPRAISAL) (JUNE 2011)

NICE is unable to recommend the use in the NHS of golimumab for the treatment of methotrexate-naïve rheumatoid arthritis (RA) because no evidence submission was received from the manufacturer or sponsor of the technology.

PACEF Recommendation:
Golimumab injection (Simponi) is designated RED-RED for the treatment of methotrexate-naïve rheumatoid arthritis.

NICE TECHNOLOGY APPRAISAL 225: *GOLIMUMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS AFTER THE FAILURE OF PREVIOUS DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS* (JUNE 2011)

Key Recommendations:

Golimumab in combination with methotrexate (MTX) is recommended as an option for the treatment of RA in adults who have responded inadequately to conventional disease-modifying anti-rheumatic drugs (DMARDs) only, including methotrexate, if it is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE TA130).

Golimumab in combination with MTX is recommended as an option for the treatment of RA in adults whose RA has responded inadequately to other DMARDs, including a TNF inhibitor if it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after the failure of a TNF inhibitor' (NICE TA195).

PACEF Recommendation:
Golimumab injection (Simponi) is licensed in combination with MTX for the treatment of moderate to severe active RA when response to DMARD therapy (including MTX) has been inadequate. It is designated RED for this indication, but not approved in MTX naïve patients.

NICE TECHNOLOGY APPRAISAL 226: *RITUXIMAB FOR THE FIRST-LINE MAINTENANCE TREATMENT OF FOLLICULAR NON-HODGKIN'S LYMPHOMA* (JUNE 2011)

Key Recommendations

Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy.

PACEF Recommendation:
Rituximab infusion (MabThera) is licensed for maintenance therapy in patients with relapsed or refractory follicular non-Hodgkin's lymphoma that has responded to induction therapy with chemotherapy (with or without rituximab) and is designated RED for this indication.

NICE TECHNOLOGY APPRAISAL 227: *ERLOTINIB MONOTHERAPY FOR MAINTENANCE TREATMENT OF NON-SMALL-CELL LUNG CANCER* (JUNE 2011)

Key Recommendations

Erlotinib monotherapy is not recommended for maintenance treatment in people with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy.

People currently receiving erlotinib monotherapy for maintenance treatment of locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

PACEF Recommendation:
Erlotinib tablets (Tarceva) are not recommended as monotherapy for maintenance treatment of locally advanced or metastatic non-small-cell lung cancer in patients with stable disease after platinum-based chemotherapy. Designation: RED-RED.

NEW TRIALS IN BRIEF

IS A MORE PROMINENT ROLE FOR LEUKOTRIENE RECEPTOR ANTAGONISTS JUSTIFIED IN THE TREATMENT OF ASTHMA?

Two parallel open-label randomised pragmatic ('real world') studies in 658 asthmatic adults (with poor asthma control or quality of life) treated in the UK, compared (1) montelukast or zafirlukast *against* inhaled corticosteroid (ICS) at step 2 and (2) ICS plus montelukast or zafirlukast *against* ICS plus long-acting beta agonist (LABA) at step 3.
Using a mini-asthma quality of life score to assess outcomes, the pre-defined equivalence criteria were met at 2 months but not at 2 years. No differences were seen in exacerbation rates, although the studies were under powered for this outcome.

PACEF Comment:
Media reporting of these studies tended to exaggerate the findings. Whilst the results are interesting, the limitations of this study (i.e. small, unblinded, absence of placebo group, cross over between treatment groups, self assessment by patients, etc) and the weight of evidence supporting current BTS/SIGN asthma guidelines leads us to recommend that the results of this study should not change current practice.

Reference: Price D et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy *NEJM* 2011; 364:1695 – 1707.

TIOTROPIUM: MORE ON THE CARDIOVASCULAR RISKS OF SPIRIVA RESPIMAT

A systematic review and meta-analysis has been conducted of five randomised controlled trials of tiotropium Respimat against placebo where mortality data was included. Tiotropium Respimat 5mcg / day was associated with a statistically significant increased risk of mortality compared with placebo (2.6% vs. 1.8%, relative risk 1.46, Number Needed to Harm 121).

PACEF Comment:
Tiotropium is available as a powder formulation (Handihaler 18mcg) and a mist inhaler (Respimat 5mcg). In November 2010 the MHRA highlighted that tiotropium mist inhaler (Respimat) might be associated with an increased risk of death compared to placebo. This is in contrast to the Handihaler where reductions in mortality, compared to placebo have been found. Reasons for the apparent difference are unclear and could be a chance finding. This study adds to mounting safety concerns around the tiotropium Respimat device. The meta-analysis was well conducted but is limited because none of the trials were set up or powered to detect differences in cardiovascular events and the number of events was small. An on-going head to head study comparing tiotropium Respimat and Handihaler may help to clarify this issue. Until further data becomes available, the Handihaler device should be used in preference to the Respimat device where inhaled tiotropium is indicated (as recommended in *PACE Bulletin* Volume 5 No 1 (January 2011)). MHRA advice that tiotropium Respimat should be used with caution in patients with known cardiac rhythm disorders should be followed. Patients with unstable cardiac disease currently prescribed tiotropium Respimat should be reviewed with a view to switching to the Handihaler device.

Reference: Singh S et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials *BMJ* 2011; 342:d3215

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND ATRIAL FIBRILLATION OR FLUTTER

Using the Danish National Registry of Patients, 32,602 people who had a first diagnosis of atrial fibrillation (AF) or flutter were identified and matched with 10 controls. NSAID use was identified using the national prescription database. After adjustment for age, sex and risk factors for AF, a significant increase in the risk of AF or flutter was found with current use of NSAID compared to no use (non-selective NSAIDs, adjusted Odds Ratio 1.17; Cox 2 inhibitors, OR 1.27).

PACEF Comment:
This study suggests that there may be a small increased risk of atrial fibrillation or flutter associated with NSAIDs, but is unable to prove an association. In light of the more established risks of NSAIDs, prescribers should continue to use NSAIDs very cautiously in older patients with a history of hypertension, coronary heart disease or heart failure.

Reference: Schmidt M et al. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case control study. *BMJ* 2011;343:d3450

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

THALIDOMIDE: RISK OF ARTERIAL AND VENOUS THROMBOEMBOLISM

Thalidomide in the form of Thalidomide Celgene is licensed for use in combination with melphalan and prednisolone as first-line treatment for patients with untreated multiple myeloma who are aged 65 years or older, or those ineligible for high dose chemotherapy. The MHRA first issued advise on the risks of Thalidomide Celgene in June 2008, highlighting the key risk of teratogenicity; the same report also highlighted other serious or potentially serious risks which included venous thromboembolism,

neutropenia, thrombocytopenia, peripheral neuropathy, syncope and bradycardia and serious skin reactions, somnolence and dizziness.

A recent global post marketing review has shown that approximately one third of all thromboembolic reactions reported in association with thalidomide were arterial; most of them were myocardial infarction (54.2%) and cerebrovascular events (19.8%). Myeloma is also a clear risk factor for thrombosis. Evidence from case reports suggests that the risk of arterial thrombotic and thromboembolic reactions is greatest during the first five months of treatment, especially in those with thromboembolic risk factors in addition to multiple myeloma.

The MHRA have issued the following advice to healthcare professionals:

- Patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism.
- Action should be taken to minimise all modifiable risk factors for thromboembolic events (e.g. smoking, hypertension and hyperlipidaemia).
- Healthcare professionals should consider venous and arterial thrombotic risk and administer antithrombotic prophylaxis for at least the first 5 months in patients commencing thalidomide.

PARACETAMOL: UPDATED DOSING SCHEDULE FOR CHILDREN

Dosing recommendations for paediatric liquids have been developed to ensure that children receive the optimum dose for their age. The new dosage instructions are detailed in the new edition of the *BNF*. The current doses consist of wide age bands with a single dose option in each band. Thus children light for their age receive a higher dose than needed for a therapeutic effect and consequently heavier children may receive a lower dose. Within hospital it is common practice to prescribe by body-weight (mg/kg). However, it is not considered practical to advocate this in the domestic environment, particularly as the majority of doses will be administered by parents or carers following dosing instructions supplied with the product. The new dosing schedule is as follows:

New Dosing Schedule

Paracetamol 120mg/5ml

Child's age	**Dose**	**Frequency (24 hours)**
2-3 months Post vaccination fever	2.5ml (60mg)	If necessary repeat after 4-6 hours
2-3 months Other causes of pain and fever if baby weighs over 4kg and was born after 37 weeks.	2.5ml (60mg)	If necessary repeat after 4-6 hours
• Do not give to babies under 2 months of age • Do not give more than 2 doses • Leave at least 4 hours between doses • If further doses are needed, talk to your doctor or pharmacist		
3-6 months	2.5ml (60mg)	4 times
6-24 months	5ml (120mg)	4 times
2-4 years	7.5ml (180mg)	4 times
4-6 years	10ml (240mg)	4 times
• Do not give more than 4 doses in any 24 hour period • Leave at least 4 hours between doses • Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist		

Paracetamol 240mg/5ml or 250mg/5ml

Child's age	Dose	Frequency (24 hours)
6-8 years	5ml (240 to 250mg)	4 times
8-10 years	7.5ml (360 to 375mg)	4 times
10-12 years	10ml (480 to 500mg)	4 times
12-16 years	10-15ml (480 to 750mg)	Up to 4 times
Adults and children over 16 years	10-20ml	Up to 4 times a day

- Do not give more than 4 doses in any 24 hour period
- Leave at least 4 hours between doses
- Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist
- Do not give to children under the age of 6 years

The MHRA have issued the following advice to healthcare professionals

- Parents and carers should be advised to follow the advice contained on current packaging.
- The new dose will be supplied with a revised patient information leaflet and packaging (entering the market by end of 2011).
- All products will be supplied with an administration device to ensure accurate administration
- Doctors may use the new dosing immediately for prescribed paracetamol products.

ADDICTION TO BENZODIAZEPINES AND CODEINE: SUPPORTING SAFER USE

Two recent reports, commissioned by the Department of Health have looked at the issue of addiction to prescribed and over the counter medicines. The reports looked at the change in prescribing patterns for benzodiazepines and "Z drugs" and the over the counter use of codeine containing products. The reports showed the decline in use of benzodiazepines used as hypnotics but increasing use as anxiolytics. There is also a gradual increase of sales of over the counter sales of codeine containing medicines.

The MHRA have issued the following reminder to healthcare professionals:

- Given the risks associated with benzodiazepine use, patients should be prescribed the lowest effective dose for the shortest time possible. Maximum duration of treatment should be 4 weeks, including the dose tapering phase.
- Over the counter codeine containing medicines should be used for short term (3 days) treatment of acute, moderate pain not relieved by paracetamol, ibuprofen or aspirin alone.

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

PIOGLITAZONE AND BLADDER CANCER: UPDATE

The Medicines and Healthcare Products Regulatory Agency (MHRA) have now completed their assessment of the risk of bladder cancer with pioglitazone and published their findings in the *Drug Safety Update* for August 2011. They have confirmed the position of the American Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) that there is a small increased risk. Standard PACEF advice from the July 2011 *PACE Bulletin* (Vol 5 No 12) remains unchanged

but has been supplemented with some additional material derived from the MHRA review:

- Prescribers should ensure that pioglitazone is not used in patients with active bladder cancer or in those with a prior history of bladder cancer or in those with uninvestigated haematuria.
- Before starting a patient on pioglitazone, the following known risk factors for development of bladder cancer should be assessed: age; current or past history of smoking; exposure to some occupational or chemotherapy agents such as cyclophosphamide; or previous irradiation of the pelvic region.
- Elderly patients should start on the lowest possible dose and be regularly monitored because of the risk of both bladder cancer and heart failure associated with pioglitazone.
- Existing patients already receiving pioglitazone should also be reviewed for risk factors associated with bladder cancer. At their next review, patients should be made aware of the risk and encouraged to remain vigilant for key symptoms such as blood or red colour in the urine, urgent need to urinate, pain while urinating or pain in the lower back or lower abdomen.
- Prescribers should review safety and efficacy of pioglitazone in individuals after 3 to 6 months (and regularly thereafter) to ensure that only those deriving sufficient benefit should continue to take it. Pioglitazone should be stopped in patients who do not respond adequately to treatment (i.e. a reduction of at least 0.5 percentage points in HbA_{1C} in six months).

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