Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

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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. Steps will be taken to ensure the widest possible distribution across Lincolnshire PCT and within United Lincolnshire Hospitals Trust and Lincolnshire Partnership Trust. Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, care pathways and other PACEF publications available through the LPCT website.

SUMMARY OF PACEF DECISIONS: AUGUST UPDATE

Drug	Indication(s)	Traffic Light Status
Adalimumab inj (Humira)	Licensed for the treatment of moderate to severe chronic plaque psoriasis where other systemic therapies, including ciclosporin, methotrexate or PUVA are contraindicated, not tolerated or ineffective.	RED
Bevacizumab infusion (Avastin)	Licensed for the first-line treatment of metastatic	RED-RED

	breast cancer in combination with paclitaxel.	
Bevacizumab infusion (Avastin)	Licensed in combination with platinum-based chemotherapy for the first-line treatment of unresectable, advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.	RED-RED
Carmustine implant (Gliadel)	Licensed for intralesional use in adults for the treatment of recurrent glioblastoma multiforme as an adjunct to surgery.	RED-RED
Cetuximab infusion (Erbitux)	Licensed in combination with radiotherapy for the treatment of locally advanced squamous carcinoma of the head and neck.	RED
Cetuximab infusion (Erbitux)	Licensed in combination with irinotecan for the treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer after failure of irinotecan-containing therapy	RED-RED
Melatonin prolonged release tablets 2mg (Circadin)	Licensed as monotherapy for the short-term treatment of primary insomnia in patients aged 55 or over	RED-RED
Rimonabant tablets 20mg (Acomplia)	Licensed as an adjunct to diet and exercise for the treatment of obese adults with a body mass index (BMI) of 30kg/m^2 and greater, or of overweight adults with a BMI of 27kg/m^2 and greater with associated risk factors such as type 2 diabetes or dyslipidaemia.	GREEN NB Third line option where orlistat and sibutramine are insufficiently effective, poorly tolerated or contra-indicated.

RED-RED: This signifies that a product is **not recommended** for prescribing in **both** primary and 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 ULHT and/or LPT **only** and has **no role in primary 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; in the coming months PACEF will be working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. 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.**

NEW DRUG ASSESSMENTS

MELATONIN PROLONGED RELEASE TABLETS (CIRCADIN)

Melatonin prolonged release 2mg tablets (Circadin) are licensed as monotherapy for the short-term treatment of primary insomnia in patients aged 55 or over; primary insomnia (i.e. insomnia not connected with any underlying medical condition) accounts for 10-30% of the total number of cases of insomnia. Melatonin is a naturally occurring hormone which is produced by the pineal gland and associated with the control of circadian rhythms and sleep regulation. Natural production of melatonin decreases with age and may explain why older patients are more prone to suffer from insomnia. Our assessment reviewed the data from the two key randomised controlled trials; these demonstrate small improvements in quality of sleep and 'morning awakeness' in patients taking melatonin prolonged release 2mg tablets compared to placebo. Both key trials were of short duration (three weeks) and had low patient numbers; further reassurance of long-term safety and low-risk of dependency can only be provided by further longer-term studies. To date, there are also no comparative studies against benzodiazepines or z-drugs. From the limited data available, tolerability seems good with the most commonly reported side effects being headache, pharyngitis, back pain and asthenia. Melatonin prolonged release (Circadin) is also three to six times more expensive than alternative hypnotics:

Approximate comparative costs

Drug	Daily dose range	Cost (£)28 days
Melatonin (Circadin)	**2mg**	**10.77***
Temazepam	10mg	£3.48
Zaleplon 5mg	5mg	£6.24
Zaleplon 10mg	10mg	£7.52
Zopiclone 3.75mg	3.75mg	£1.87
Zopiclone 7.5mg	7.5mg	£1.76
Zolpidem 5mg	5mg	£1.79
Zolpidem 10mg	10mg	£2.23

***** supplied in packs of 21 tablets

PACEF Recommendation:
PACEF were concerned about the poor quality of the trial data supporting the use of melatonin prolonged release tablets: both key trials were against placebo, of short duration and had low patient numbers; any benefits demonstrated were marginal and inconclusive. In addition, none of trials provided comparative data against commonly used alternative treatments such as benzodiazepines or z-drugs. The cost differential was also problematic with Circadin costing three to six times as much as established alternatives. As a result of this, melatonin prolonged release tablets 2mg (Circadin) were

designated RED-RED. Non-pharmacological approaches to the treatment of insomnia are advocated first line. Where a hypnotic is indicated, a short course (two to four weeks) of a hypnotic of low acquisition cost (e.g. temazepam or zopiclone) is preferred. Hypnotics should only be prescribed where insomnia is severe, disabling and subjecting the individual to extreme distress.

NICE TECHNOLOGY APPRAISAL 144: *RIMONABANT FOR THE TREATMENT OF OVERWEIGHT AND OBESE ADULTS* (JUNE 2008)

NICE have now completed their appraisal of rimonabant (Acomplia). The evidence of effectiveness derives from four randomised controlled trials comparing rimonabant to placebo. In these trials, the active drug was associated with a statistically significant greater weight loss than placebo at both one and two years. Additional beneficial effects emerging from trials include: reduced systolic BP, increased HDL-C and reduced triglycerides, fasting plasma glucose and HbA1c. There is no evidence of efficacy or safety beyond the length of the longest trial (2 years) and no comparative data against the key competitor products, orlistat and sibutramine. The absence of long-term data means that claims of long-term beneficial outcomes such as reduced risk of cardiovascular and diabetic events cannot be substantiated.

NICE make the following recommendations:

- Rimonabant, (Acomplia) within its licensed indications, is recommended as an adjunct to diet and exercise for adults who are obese or overweight and who have had an inadequate response to, or are intolerant of, or are contraindicated to orlistat or sibutramine.
- Rimonabant should be continued beyond 6 months only if the person has lost at least 5% of their initial body weight since starting treatment.
- Rimonabant should be discontinued if the person returns to their original weight while on treatment.
- Rimonabant should not be continued beyond 2 years without a formal clinical assessment and discussion of risks and benefits with the person receiving treatment.

PACEF Recommendation:

Prescribers are reminded that rimonabant should be reserved for third line use as an adjunct to diet and exercise for the treatment of obese adults (defined as having a body mass index (BMI) of 30kg/m^2 and greater) or of overweight adults (BMI of 27kg/m^2 and greater) with associated risk factors such as type 2 diabetes or dyslipidaemia. Concurrent participation in lifestyle, diet and exercise programmes is essential in order to achieve maximum benefit. Rimonabant should only be used where orlistat and sibutramine are not tolerated, insufficiently effective or contra-indicated. Steatorrhoea with orlistat should not be classified as intolerance, but as a consequence of failure to follow dietary advice. Prescribers are also reminded of recent MHRA safety advice on rimonabant previously published in *PACE Bulletin*, Vol 2, No 10 (see box below). Subject to all of these constraints, rimonabant is classified as GREEN.

MHRA Advice on Rimonabant and Depressive Reactions

The MHRA has issued the following advice to healthcare professionals: Depressive reactions may occur in up to 10% of patients treated with rimonabant. Patients who have no obvious risk factors, apart from obesity itself, may be affected. The evidence suggests that many patients who develop

such reactions will do so within 2 weeks of starting treatment. Rimonabant is contraindicated in patients with ongoing major depression or those taking antidepressants. Prescribers are encouraged to take a detailed history from patients before prescribing rimonabant to assess risk factors for psychiatric reactions, particularly depression.

NICE TECHNOLOGY APPRAISAL 145: *CETUXIMAB FOR THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CANCER OF THE HEAD AND NECK* (JUNE 2008)

The NICE recommendation is as follows:

- Cetuximab in combination with radiotherapy is recommended as a treatment option only for patients with locally advanced squamous cell cancer of the head and neck whose Karnofsky performance-status score is 90% or greater and for whom all forms of platinum-based chemoradiotherapy treatment are contraindicated.

PACEF Recommendation:
Subject to licensed indications and NICE restrictions, cetuximab infusion (Erbitux) is designated RED.

NICE TECHNOLOGY APPRAISAL 146: *ADALIMUMAB FOR THE TREATMENT OF ADULTS WITH PSORIASIS* (JUNE 2008)

The NICE recommendation is as follows:

- Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met: (1) The disease severity as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10; (2) The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant of, or has a contraindication to, these treatments.
- Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either a 75% reduction in PASI score (PASI 75) from when treatment is started or a 50% reduction in PASI score (PASI 50) and a five point reduction in DLQI from start of treatment.

PACEF Recommendation:
Subject to licensed indications and NICE restrictions, adalimumab (Humira) is designated RED.

NICE TECHNOLOGY APPRAISAL 147: *BEVACIZUMAB FOR THE FIRST-LINE TREATMENT OF METASTATIC BREAST CANCER (TERMINATED APPRAISAL)* (JUNE 2008)

The NICE recommendation is as follows:

- Bevacizumab in combination with paclitaxel is not recommended for the first-line treatment of metastatic breast cancer.

- This is due to the fact that the manufacturer's submission to NICE did not include a full economic analysis. When challenged, the manufacturer informed NICE that preliminary calculations revealed that the treatment regimen of bevacizumab and paclitaxel was unlikely to be regarded as cost-effective for metastatic breast cancer compared with paclitaxel monotherapy. As a result of this, the Appraisal has been terminated.

PACEF Recommendation:
Bevacizumab (Avastin) in combination with paclitaxel is not recommended for the first-line treatment of metastatic breast cancer and is designated RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL 148: *BEVACIZUMAB FOR THE TREATMENT OF NON-SMALL-CELL LUNG CANCER (TERMINATED APPRAISAL)* (JUNE 2008)

The NICE recommendation is as follows:

- Bevacizumab is not recommended for use in addition to platinum-based chemotherapy for the first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small-cell lung cancer (other than predominantly squamous cell histology)
- This is due to the fact that the manufacturer have informed NICE that they do not intend to launch or promote bevacizumab for the lung cancer indication and as a result will not be making an evidence submission. As a result of this, the Appraisal has been terminated.

PACEF Recommendation:
Bevacizumab (Avastin) in combination with platinum-based chemotherapy is not recommended for the first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small-cell lung cancer and is designated RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL 149: *CARMUSTINE IMPLANTS FOR THE TREATMENT OF RECURRENT GLIOBLASTOMA MULTIFORME (TERMINATED APPRAISAL)* (JUNE 2008)

The NICE recommendation is as follows:

- Carmustine implants are not recommended as an adjunct to surgery in patients with recurrent glioblastoma multiforme.
- Following the publication of NICE TA121 (*Carmustine implants and temozolamide for the treatment of newly diagnosed glioma* (July 2007)) the manufacturer is of the view that most patients will have received treatment with carmustine implants before subsequent surgery for recurrent glioblastoma. The only data available does not reflect this current practice and cannot be used to perform a cost-effectiveness assessment of this present indication. As a result of this, the Appraisal has been terminated.

PACEF Recommendation:
Carmustine implant (Gliadel) is not recommended as an adjunct to surgery in patients with recurrent glioblastoma multiforme and has been designated as RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL 150: *CETUXIMAB FOR THE TREATMENT OF METASTATIC COLORECTAL CANCER FOLLOWING FAILURE OF OXALIPLATIN-CONTAINING CHEMOTHERAPY (TERMINATED APPRAISAL)* (JUNE 2008)

The NICE recommendation is as follows:

- Cetuximab is not recommended for the treatment of colorectal cancer following failure of oxaliplatin-containing chemotherapy because no evidence submission was received from the manufacturer or sponsor of the technology. The manufacturer did not make the submission due to lack of evidence of cost-effectiveness for this indication. As a result of this, the Appraisal has been terminated.

PACEF Recommendation:
Cetuximab is not recommended for the treatment of colorectal cancer following failure of oxaliplatin-containing chemotherapy and has been designated as RED-RED for this indication.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: DRUG SAFETY UPDATE (JULY 2008)

VARENICLINE: SUICIDAL THOUGHTS AND BEHAVIOUR

Possible links between varenicline and suicidal thoughts and behaviour have been reviewed in a previous issue of the *PACE Bulletin* (Vol 2, No 3). Most recently the MHRA have undertaken a detailed review of UK Yellow Card data and found that suicide-related events have been reported in patients taking varenicline who have no known pre-existing psychiatric condition. As a result of this they have issued the following advice:

- Patients should be told to stop treatment and contact their doctor immediately if they develop suicidal thoughts and behaviour.
- Varenicline should be stopped immediately if agitation, depressed mood, or changes in behaviour are observed that are of concern to the patient, family or caregivers.
- The safety and efficacy of varenicline in people with serious psychiatric illness have not been established. Patients who have a history of psychiatric illness should be monitored closely while taking varenicline.

BISPHOSPHONATES AND ATRIAL FIBRILLATION

The MHRA have reported on concerns related to a possible link between bisphosphonates and atrial fibrillation. They conclude that the balance of risks and benefits for bisphosphonates remains favourable. We conducted our own review of the trial evidence and the results are reported below:

In 2007 the *New England Journal of Medicine* published a 3-year randomized controlled trial (RCT) known as the HORIZON study which looked at once yearly intravenous (IV) zoledronic acid 5mg (3875 analysed) against placebo (3861 analysed) for the treatment of postmenopausal osteoporosis [1]. Whilst the yearly infusion significantly decreased the risk of vertebral, hip and other fractures the authors reported that *serious* atrial fibrillation (AF) occurred more frequently in the treatment group. A Number Needed to Harm (NNH) of 130 was calculated (i.e. 130

patients would have to be treated with IV zoledronic acid for 3 years to see one extra case of serious AF that would not have otherwise occurred if the patients had been given placebo). The majority of these patients (47/50) experienced serious AF more than 30 days after the infusion which rules out any immediate effect of the IV dose. This study prompted other researchers to see if this effect was seen in orally administered bisphosphonates.

In March 2008 the *BMJ* published online a retrospective population based case-controlled study of patients with AF in Denmark [2]. The rate of ***current*** bisphosphonate use (alendronic acid or etidronate) in the AF group was 3.2% compared to 2.9% in the control group; this trend suggested that patients were slightly more likely to be on a bisphosphonate if they had AF. However, when the groups were adjusted for cardiovascular and various other AF risk factors, the trend suggested that patients with AF were slightly less likely to be on a bisphosphonate. The authors concluded that there was no evidence that oral bisphosphonate use increased the risk of AF.

A subsequent paper in *Archives of Internal Medicine* in April 2008 provided another retrospective population-based case-controlled study [3]. The authors looked at whether alendronic acid had ever been used (either current or former use) in 719 women with AF and 996 controls in Washington State. More AF patients than controls had ever used alendronate (6.5% [n=47] vs 4.1% [n=40]; *P*=.03). Compared with never use of any bisphosphonate, ever use of alendronate was associated with a higher risk of incident AF after adjustment for the matching variables. The authors estimated that 3% of incident AF in this population might be explained by alendronate use. There was no relationship to dose or duration of the drug which argues against any pharmacological effect of the alendronic acid.

The evidence that oral bisphosphonates increase the risk of AF is limited and conflicting. If there is an effect it appears to be very small and unrelated to dose and duration. It is also not clear whether this is a class effect or not. A prospective RCT specifically looking at AF and rigorous postmarketing surveillance is needed to determine whether the effect is real and whether all bisphosphonates are implicated. A recent *BMJ* editorial, summarising the available evidence, asked what the implications were for clinicians faced with their older female patients with fractures and osteoporosis:

> For now, beyond taking the patient's pulse and ordering an electrocardiogram when it is irregular, available evidence suggests that business should carry on as usual—the risk of atrial fibrillation associated with oral bisphosphonates seems to be vanishingly small if it exists at all, and it is unlikely to ever offset the confirmed benefits of these drugs in the prevention of fractures.[4]

PACEF Recommendation:
Current evidence does not present any compelling reason to alter our recommendation that weekly generic alendronic acid should be the first line bisphosphonate of choice. MHRA advice is that the balance of risks and benefits of bisphosphonates remains favourable.

References

1. Black DM et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *NEJM* 2007; **356:** 1809-22
2. Sørensen HT et al Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. *BMJ* published online 11 Mar 2008 doi: 10.1136/bmj.39507.551644.BE
3. Heckbert SR et al. Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med* 2008;**168:** 826-831
4. Majumdar SR Oral bisphosphonates and atrial fibrillation. *BMJ* 2008; **336:** 784-5

ROTIGITINE PATCHES; NEW PRESCRIBING AND STORAGE REQUIREMENTS

PACEF recently approved the use of rotigitine patches (Neupro) for the treatment of Parkinson's disease (see *PACE Bulletin*, Vol 1, No 8). The MHRA have raised concern over the appearance of crystalline rotigitine visible within some of the patches. There is a theoretical possibility that this may reduce clinical efficacy, although there is no evidence to date that this has occurred. Advice to healthcare professionals is as follows:

- Healthcare professionals should be alert to the risk of reduced or lack of efficacy of transdermal rotigitine and report any incidents through the Yellow Card Scheme.
- Patients should be informed that they must not stop using their rotigitine patches even if they notice snowflake patterns in the patch. Abrupt withdrawal has been associated with a syndrome resembling neuroleptic malignant syndrome or akinetic crisis. If crystals are identified within the patch, the patient should notify a healthcare professional.
- Patients should be advised to store their rotigitine patches in the refrigerator; refrigeration seems to reduce crystal development.

NATIONAL PATIENT SAFETY AGENCY (NPSA) RAPID RESPONSE REPORT – RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES (JANUARY 2008)

The NPSA have issued this Rapid Response Report to ensure that the prescribing, dispensing and administration of oral anti-cancer medicines is carried out and monitored to the same standard as injectable therapy. They have made the following recommendations to healthcare professionals:

- All treatment should be initiated by a cancer specialist.
- All oral anticancer medicines should be prescribed only in the context of a written protocol and treatment plan.
- Non-specialists who prescribe or administer on-going oral anticancer medication should have ready access to appropriate written protocols and treatment plans including guidance on monitoring and treatment of toxicity.
- Staff dispensing oral anti-cancer drugs should be able to confirm that the prescribed dose is appropriate for the patient, and that the patient is aware of the required monitoring arrangements, by having access to information in the written protocol and treatment plan from the hospital where treatment is initiated and advice from a pharmacist with experience in cancer treatment in that hospital.
- Patients should be fully informed and receive both verbal and written information about their therapy from the initiating hospital. This advice should include contact details for specialist advice and details of the intended regimen, treatment plan and monitoring.
- This information also needs to be accessible to pharmacists and dispensary staff to enable them to have sufficient information to enable them to comply with the recommendations for the safe dispensing of oral cancer drugs.

PACEF Recommendations:

(1) All GPs and non medical prescribers (NMPs) should refuse any NEW requests to prescribe oral anticancer drugs for the treatment of cancers unless they have ready access to written treatment protocols or treatment plans which must include full details of monitoring requirements and treatment of toxicity.

(2) All GPs and community based nursing staff should not accept responsibility to administer any oral anticancer medication used in the treatment of cancers unless they have ready access to written treatment protocols or treatment plans which must include full details of monitoring requirements and treatment of toxicity.

(3) All community pharmacists and general practice run dispensary services should not accept any NEW requests to dispense any oral anticancer drug being used for the treatment of cancers unless they have ready access to written treatment protocols or treatment plans from the hospital from where the treatment was initiated and are able to confirm that the prescribed dose is appropriate for the patient.

(4) The onus should be on secondary and tertiary care based services to ensure they are able to provide sufficient information to ensure the safe prescribing/dispensing and administration of oral anti-cancer drugs in a primary care setting.

(5) All GP and NMPs should continue to support patients who are currently receiving oral anticancer medicines initiated before 22nd July 2008. Every effort however should be made to ensure that the prescriber has access to written treatment protocols/treatment plans including full details of monitoring requirements and all prescribers must be clear as to what their ongoing responsibilities are.

(6) All prescribing of oral anti-cancer drugs for non-cancer indications should be supported by the development of shared care protocols. A particular need has been identified for the development of SCGs for hydroxycarbamide and mercaptopurine.

Acknowlegements

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Stephen Gibson
Head of Prescribing and Medicines Management
Lincolnshire PCT

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