Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

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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. 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: JULY UPDATE

Drug	Indication(s)	Traffic Light Status
Adalimumab (Humira)	Severe active ankylosing spondylitis subject to NICE criteria	RED
Epoetin alfa (Eprex), Epoetin beta (NeoRecormon) Darbepoetin alfa (Aranesp)	In combination with IV iron as an option for the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia. In combination with IV iron for people who cannot be given a blood transfusion and	RED RED

	who have profound cancer treatment-induced anaemia that is likely to impact on survival.	
Etanercept (Enbrel)	Severe active ankylosing spondylitis subject to NICE criteria	RED
Human Papillomavirus Vaccine (Cervarix and Gardasil)	Prevention of high-grade intraepithelial neoplasia and cervical cancer causally related to HPV types 16 and 18.	RED-RED
Infliximab (Remicade)	Severe active ankylosing spondylitis	RED-RED
Paricalcitol capsules (Zemplar)	Licensed for the prevention and treatment of secondary hyperparathyroidism (SHPT) associated with chronic renal insufficiency (chronic kidney disease Stages 3 and 4) and chronic renal failure (chronic kidney disease Stage 5) in patients on haemodialysis or peritoneal dialysis.	RED-RED
Ropinirole immediate release tablets (Requip)	Licensed as monotherapy or as an adjunct to levodopa in idiopathic Parkinson's disease.	GREEN
Ropinirole prolonged release tablets (Requip XL)	Licensed as monotherapy or as an adjunct to levodopa in idiopathic Parkinson's disease in patients already adequately controlled on ropinirole immediate release tablets.	RED-RED
Venlafaxine modified release 75mg (Efexor XL)	Generalised anxiety disorder Social phobia	AMBER N.B. Only initiate on the advice of specialist mental health services. No shared care guideline is required

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

PARICALCITOL CAPSULES (ZEMPLAR)

Paricalcitol (Zemplar) is an oral formulation of a synthetic, biologically active vitamin D analogue and belongs to a group of drugs known as the Vitamin D Receptor Activators (VDRAs); other drugs in the group include calcitriol and alfacalcidol. It is licensed for the prevention and treatment of secondary hyperparathyroidism (SHPT) associated with chronic renal insufficiency (chronic kidney disease Stages 3 and 4) and chronic renal failure (chronic kidney disease Stage 5) in patients on haemodialysis or peritoneal dialysis.

Data from randomised placebo controlled trials show that paricalcitol capsules are an effective treatment for SHPT, but there are no comparative studies against other VDRAs. The yearly acquisition cost of paricalcitol capsules is 7 to 20 times higher than alternative agents depending on the dose prescribed.

PACEF Recommendation
The lack of comparative studies against other VDRAs made it very difficult for PACEF to assess the comparative efficacy and tolerability of oral paricalcitol. The extremely high acquisition cost in comparison to alternatives also gave cause for concern. As a result of these factors, paricalcitol (Zemplar) is designated: RED-RED.

ROPINIROLE PROLONGED RELEASE TABLETS (REQUIP XL)

Ropinirole (Requip) is a dopamine receptor agonist licensed as monotherapy or as an adjunct to levodopa in idiopathic Parkinson's disease. The immediate release tablet has previously been reviewed by PACEF and designated as GREEN. The patent on this formulation is due to expire in July 2011. Most recently, a prolonged release tablet formulation of ropinirole (Requip XL) has been launched that is licensed as monotherapy or as an adjunct to levodopa in idiopathic Parkinson's disease in patients already adequately controlled on ropinirole immediate release tablets. This prolonged release formulation offers the advantage of once daily dosing over the thrice daily regime of the immediate release formulation. There appears to be no published evidence to suggest additional benefits in control of symptoms compared to the immediate release preparation or alternative dopamine agonists. Direct price comparison is difficult due to the range of possible doses of the standard release product; use of the prolonged release product appears to offer only very minimal cost benefits over existing dosage forms.

PACEF Recommendation
Ropinirole prolonged release (Requip XL) has no proven additional benefits over the immediate release formulation other than its once daily dosing regime. PACEF were concerned that commitment to this product at this stage

could result in a reduction in generic savings following the patent expiry of immediate release ropinirole (Requip) in the future. As a result of this ropinirole prolonged release (Requip XL) is designated RED-RED.

NEW INDICATION ASSESSMENT

VENLAFAXINE (EFEXOR XL) FOR GENERALISED ANXIETY DISORDER AND SOCIAL PHOBIA

Venlafaxine is a well-established serotonin and noradrenaline re-uptake inhibitor (SNRI) antidepressant. Since 2001, venlafaxine 75mg modified release (Efexor XL) has been licensed for the treatment of generalised anxiety disorder (GAD) in adults. Most recently, the same formulation has been additionally licensed for the treatment of social phobia in adults. The standard dose for both indications is 75mg daily.

NICE Clinical Guideline 22 (amended in April 2007) provides guidance on the treatment of GAD. Recommended first line options are self help, psychological support (Cognitive Behavioural Therapy) and pharmacological treatment with a selective serotonin re-uptake inhibitor (SSRI). Paroxetine and escitalopram are the two SSRIs licensed for the treatment of GAD, but NICE guidance allows for the use of other SSRIs. Venlafaxine is identified by NICE as a second-line option following the failure of two SSRIs or the unsuitability of SSRI treatment.

In the treatment of social phobia, venlafaxine XL 75mg emerges from trials as equally effective to paroxetine; doses above 75mg seem to offer no further increase in efficacy. There are currently no NICE clinical guidelines covering the pharmacological treatment of this condition. Paroxetine and escitalopram are both licensed for the treatment of social phobia, although there is no evidence demonstrating any particular advantage over other SSRIs. SSRIs currently have the best evidence for efficacy in the long-term treatment of social phobia. British Society of Psychopharmacology guidelines for the treatment of anxiety disorders recommend an SSRI for first-line drug treatment of social phobia, but do not clearly distinguish between the various available treatments. Venlafaxine is recommended where other treatments have failed. The choice of whether or not venlafaxine should be used following failure of SSRI treatment remains a decision for specialist mental health services.

PACEF Recommendation

Venlafaxine 75mg modified release (Efexor XL) is designated as AMBER for both generalised anxiety disorder and social phobia. For both of these indications, venlafaxine XL should only be initiated on the advice of specialist mental health services. No shared care guideline is required. Further work will be undertaken with Lincolnshire Partnership Foundation Trust (LPFT) over the coming weeks to clarify the GAD treatment pathway and the role of venlafaxine XL for this indication in primary care.

INTRODUCTION OF HUMAN PAPILLOMAVIRUS (HPV) VACCINE INTO THE NATIONAL IMMUNISATION PROGRAMME

As you will already be aware following a letter from the Chief Medical Officer, **HPV vaccination is to be introduced into the national immunisation programme from the beginning of the 2008/09 school year**. The immunisation will be offered routinely to all 12 to 13 year old girls (school year 8) to protect them against the future risk of cervical cancer. **The first cohort of girls to be immunised will be**

those born between 1st September 1995 and 31 August 1996 (school year 8 in 2008/09); in practice, any girl in school year 8 will be offered HPV immunisation, regardless of age. A schools based programme has been recommended. **A two-year catch-up campaign will start from the beginning of the 2009/10 school year for all girls aged up to 18 years (i.e. 17 years and 364 days) at 31st August 2009.** All girls born between 1st September 1991 and 31st August 1993 (school years 12 and 13 in academic year 2009/10) will be offered immunisation from the beginning of the 2009/10 school year. All girls born between 1st September 1993 and 31st August 1995 (school years 11 and 12 in academic year 2010/11) will be offered the vaccine from the beginning of the 2010/11 school year. More information on the catch-up campaign will follow at a later date. It has been estimated that HPV vaccination will save the lives of 400 women each year.

Two HPV vaccines are currently available (Gardasil and Cervarix) that have been shown to protect against the two high-risk HPV types (16 and 18) that cause 70% of cervical cancers. A three-dose course is required over about six months. **The vaccine to be utilized as part of the national programme will be supplied free of charge to PCTs.** Any FP10 prescribing that occurs from general practice in addition to the national programme will feature as expenditure against practice and PBC Cluster prescribing budgets; the NHS price of each course of three vaccinations is £241.50. **The Joint Committee on Vaccination and Immunisation (JCVI) have advised that a catch-up campaign for all women aged 18 years and over would not be cost-effective. However, they have advised the Dept of Health that immunisation could benefit some individuals. This proposal remains under consideration at the Dept of Health and further advice will be issued on this patient group in due course.** The national cervical screening programme will remain unchanged by the introduction of the new vaccination programme.

Further clinical information can be accessed through a new HPV Vaccine chapter written for *Immunisation against Infectious Disease* which is now available on the Dept of Heath website (www.dh.gov.uk/greenbook).

PACEF Recommendation:
Details of the new HPV national vaccination programme have now been announced. All girls who are likely to qualify for vaccination either as part of the first cohort or the two-year catch-up campaign should be advised to wait to receive the vaccination through the national programme. The JCVI have advised that a catch-up campaign for all women aged 18 and over would not be cost-effective, but have recommended that the DoH should consider sanctioning vaccination for further higher-risk individuals. This is currently under consideration at the Department. Until further guidance is received, existing PACEF guidance on HPV vaccination remains in place:

Both of the HPV vaccines currently available (Gardasil and Cervarix) are designated as RED-RED and should not be prescribed under any circumstances in primary care, either on the NHS or privately. As both vaccines are licensed for use and have not been black-listed by the NHS, a GP would potentially be in breach of regulations if they offered the vaccine on private prescription.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 142: *EPOETIN ALFA, EPOETIN BETA AND DARBEPOETIN ALFA FOR CANCER TREATMENT- INDUCED ANAEMIA* (MAY 2008)

The potential side effects of erythropoietin analogues in people with anaemia receiving treatments for cancer have recently been reviewed by the European Medicines Agency (EMEA). This review raised concerns over an increased risk of serious cardiovascular complications in people with chronic renal failure and a possible effect on tumour progression in people with cancer.

This NICE TA makes the following recommendations:

- Erythropoietin analogues are not recommended for routine use in the management of cancer treatment-induced anaemia, except in the circumstances described below:
    1. Erythropoietin analogues are recommended in combination with IV iron as an option for the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8g per 100ml or lower.
    2. Erythropoietin analogues in combination with IV iron may be considered for people who cannot be given a blood transfusion and who have profound cancer treatment-induced anaemia that is likely to impact on survival.
- In the circumstances outlined in (1) and (2), the erythropoietin analogue with the lowest acquisition cost should be used.

PACEF Recommendation

Epoetin alfa (Eprex), epoetin beta (NeoRecormon) and darbepoetin alfa (Aranesp) are all designated RED for these indications within the constraints specified. PACEF were unable to identify the drug of lowest acquisition cost as the NHS price of each drug was broadly similar. Variation in hospital prices may result in a clearer conclusion within secondary care. Recent safety concerns raised by the EMEA and the Medicines and Healthcare products Regulatory Agency (MHRA) are likely to preclude future shared care development.

NICE TECHNOLOGY APPRAISAL 143: *ADALIMUMAB, ETANERCEPT AND INFLIXIMAB FOR ANKYLOSING SPONDYLITIS* (MAY 2008)

This NICE TA makes the following recommendations:

- Adalimumab (Humira) or etanercept (Enbrel) are recommended as treatment options for adults with severe active ankylosing spondylitis (AS) only if: (1) The patient's disease satisfies the modified New York criteria for diagnosis of AS; (2) There is confirmation of sustained active spinal disease demonstrated by a score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) **and** at least 4cm on the 0 to 10cm Visual Analogue Scale (VAS) (these should be demonstrated on two occasions at least 12 weeks apart without any change of treatment); (3) Conventional treatment with two or more NSAIDs taken sequentially at maximum tolerated or recommended dosage for 4 weeks has failed to control symptoms.

- The response to adalimumab or etanercept should be assessed 12 weeks after treatment is initiated; treatment should only be continued in the presence of an adequate response.
- Subject to an adequate response, patients should have their condition monitored at 12 week intervals thereafter.
- If the response is not adequate a repeat assessment should be made after a further 6 weeks. If the response is not adequate at this point, treatment should be discontinued.
- For patients shown to be intolerant to either adalimumab or etanercept before the end of the initial 12 week assessment period, the alternative agent of the pair is recommended. An alternative TNF alfa inhibitor should not be prescribed for patients who have failed to achieve an adequate response with either adalimumab or etanercept.
- Adalimumab or etanercept for severe active ankylosing spondylitis should be intiated and supervised only by specialist physicians experience in the diagnosis of AS.
- Infliximab (Remicade) is not recommended for AS.

PACEF Recommendation
Adalimumab (Humira) and etanercept (Enbrel) are classified as RED for this indication. Both drugs are administered as SC injection and should only be prescribed under specialist supervision. A shared care guideline proposal may be considered at a later date, but, at present, shared care has not been approved. Infliximab (Remicade) is designated as RED-RED for this indication and should not be prescribed for ankylosing spondylitis.

MHRA SAFETY UPDATE: NICORANDIL (IKOREL) (JUNE 2008)

Nicorandil (Ikorel) is licensed for the prevention and treatment of angina. Mouth ulceration is widely recognised as a side effect. Recent reports have shown that severe ulceration may occur within any region of the gastrointestinal tract and can be so severe that it leads to perforation. As a result of these reports, the MHRA has issued the following advice:

- GPs and other healthcare professionals should consider nicorandil treatment as a possible cause in patients who present with symptoms of gastrointestinal ulceration, including perianal ulceration.
- Ulcers that result from nicorandil therapy are refractory to treatment including surgery; they respond only to withdrawal of nicorandil.
- Nicorandil withdrawal should take place only under the supervision of a cardiologist.

PACEF Recommendation
Nicorandil is a treatment that is commonly prescribed in Lincolnshire. Prescribers are urged to remain alert to this potentially serious safety concern.

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