NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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What's new this month?

- **Rifaximin 200mg tablets (Xifaxanta) have been designated RED-RED for travellers' diarrhoea. Private prescribing of an anticipatory course is endorsed for people travelling to areas of high risk where better established alternatives are deemed to be inappropriate due to patient factors or local resistance patterns (see page 3).**
- **Tacrolimus ointment 0.03% and 0.1% (Protopic) is designated AMBER without shared care for both treatment of moderate to severe atopic dermatitis and for the prevention of flares and the prolongation of flare free intervals (see page 4).**
- **Roflumilast (Daxas) is not recommended for the treatment of severe chronic obstructive pulmonary disease and is designated RED-RED (see page 7).**
- **Apixaban (Eliquis) has been approved by NICE for the prevention of venous thromboembolism after total hip or knee replacement in adults and is designated RED (see page 8).**
- **Updated editions of the *Wound Management Formulary* and the *Policy Relating to the Prescribing, Supply, Storage and Disposal of Controlled Drugs in Primary Care* are now available (see page 8).**
- ***Lincolnshire Medication Procedure Guidance (Adult Care Homes)* is now available (see page 8).**

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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: *MARCH 2012 UPDATE*

Drug	Indication(s)	Traffic Light Status
Apixaban 2.5mg tablets (Eliquis)	Licensed for the prophylaxis of venous thromboembolism in adults after hip or knee replacement surgery	RED
Bevacizumab intravenous infusion (Avastin)	Licensed for use in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.	RED-RED
Cetuximab intravenous infusion (Erbitux)	Licensed for use as monotherapy or as combination chemotherapy for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.	RED-RED
Dasatinib tablets (Sprycel)	Licensed for the treatment of chronic, accelerated or blast-crisis phase chronic myeloid leukaemia CML in adults.	RED-RED
Imatinib tablets (Glivec)	Licensed for the treatment of Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults.	RED (standard dose) High dose imatinib treatment is not approved by NICE
Nilotinib capsules (Tasigna)	Licensed for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults.	RED
Panitumumab intravenous infusion (Vectibix)	Licensed for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.	RED-RED
Rifaximin (Xifaxanta) 200mg tablets	Licensed for the treatment of non-invasive travellers' diarrhoea	RED-RED Could be prescribed privately for people travelling to areas of high risk where better established alternatives are deemed to be inappropriate due to patient factors or local resistance patterns.
Rituximab intravenous infusion (MabThera)	Licensed in combination therapy for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people.	RED
Roflumilast tablets 500 microgram (Daxas)	Licensed as an adjunct to bronchodilators for the maintenance treatment of patients with severe COPD associated with chronic bronchitis and a history of chronic exacerbations	RED-RED
Tacrolimus ointment 0.03% and 0.1% (Protopic)	Licensed for the treatment of moderate to severe atopic dermatitis in children aged 2 and above (0.03%) and adults who have not adequately responded to or are intolerant of conventional therapies such as topical corticosteroids	AMBER without shared care
Tacrolimus ointment 0.03% and 0.1% (Protopic)	Licensed for the maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring more than four or more times a	AMBER without shared care

	year).	

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: *RIFAXIMIN 200MG TABLETS (XIFAXANTA) FOR TRAVELLERS' DIARRHOEA*

Rifaximin (Xifaxanta) is a rifampicin related antibiotic licensed for the treatment of non-invasive travellers' diarrhoea (not complicated by fever and blood in the stools). PACEF reviewed the results of three clinical studies. One was a dose finding study against placebo in adults with travellers' diarrhoea that demonstrated a 50% reduction in duration of diarrhoea and confirmed the dose as 200mg every eight hours for a period of three days. The second study confirmed superiority to placebo in terms of reduction in duration of diarrhoea and showed some additional benefit from concurrent therapy with loperamide. The final study compared rifaximin 200mg every eight hours for 3 days with ciprofloxacin 500mg twice daily for the same duration in adult patients with acute diarrhoea. Rifaximin emerged as comparable in efficacy to ciprofloxacin in non-invasive acute diarrhoea, although in patients with invasive intestinal bacterial pathogens, ciprofloxacin was more effective. Rifaximin is not recommended for diarrhoea associated with invasive organisms such as *Campylobacter* and *Shigella.*

One advantage of rifaximin is that very little active drug is absorbed from the gastrointestinal tract. Low absorption results in a lower incidence of systemic adverse effects and drug interactions; it also reduces the risk of developing antimicrobial resistance.

When travelling to geographical areas deemed to be high risk, the main aim is for travellers to avoid risk factors associated with waterborne infection such as potentially contaminated food and water supplies and by maintaining vigilance with personal hygiene. The Health Protection Agency (HPA) advise that a private prescription for a three day course of ciprofloxacin could be provided for those visiting remote areas or those considered to be at high risk; this course could be taken if symptoms develop. There is no reference to rifaximin in the latest HPA guidance issued in January 2012. There are already areas where there is increased resistance to ciprofloxacin; in these areas alternatives such as levofloxacin, azithromycin and bismuth salicylate (Pepto Bismol) are sometimes used.

ULHT microbiology do not advise treating traveller's diarrhoea with an antibiotic once the patient returns to the UK unless microbiology sensitivities indicate a particular treatment. Sensitivity testing conducted locally does not currently include rifaximin.

In terms of comparative cost, rifaximin is much more expensive than alternative antibacterials as illustrated below:

Drug	Daily dose range	Cost (£)per course
Rifaximin 200mg tablets (Xifaxanta)	**200mg every 8 hours for 3 days**	**£15.15**
Ciprofloxacin tablets (generic)	750mg stat dose	0.24
	500mg twice daily for 3 days	0.55
Azithromycin tablets/capsules (generic)	1 gram stat dose	£9.64 (4 x 250mg)
Levofloxacin tablets	500mg daily for 3 days	£7.76

Rifaximin has also been used off license for the management of symptoms associated with irritable bowel syndrome (IBS) and for the treatment of hepatic encephalopathy. An application to extend the license to cover use in the treatment of hepatic encephalopathy is expected in 2013.

PACEF Recommendation:
Rifaximin (Xifaxanta) is not currently recommended by the HPA for use in the treatment of non-invasive travellers' diarrhoea. There are a number of alternatives that are currently endorsed by the HPA and should be used preferentially. Wherever an anticipatory course of antibacterial treatment is issued for a patient visiting a geographical area deemed to be high risk, this should be on private prescription. Rifaximin (Xifaxanta) is designated RED-RED for this indication, but could be issued privately where better established alternatives are deemed to be inappropriate due to patient factors or local resistance patterns. Off license use of rifaximin is not currently recommended although new licensed indications will be reviewed by PACEF as they appear.

RAPID DRUG ASSESSMENT: *TACROLIMUS OINTMENT 0.03% AND 0.1% (PROTOPIC) FOR MAINTENANCE TREATMENT OF MODERATE TO SEVERE ATOPIC DERMATITIS*

Tacrolimus ointment 0.03% and 0.1% (Protopic) now hold a range of different licensed indications. The 0.03% preparation is for use in children aged over 2 years and the 0.1% for adults and children aged over 16 years; both are licensed for:

- the **treatment of moderate to severe atopic dermatitis** in those who have not adequately responded to or are intolerant of conventional therapies such as topical corticosteroids.
- the **maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare free intervals** in patients experiencing a high frequency of disease exacerbations (i.e. occurring more than four or more times a year), who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared or mildly affected).

NICE have approved topical tacrolimus for the treatment of atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side effects (e.g. skin atrophy) (see NICE TA 82 *Tacrolimus and pimecrolimus for atopic eczema* (August 2004)). NICE also published Clinical Guideline 57 in December 2007 which covered the management of atopic eczema in children. This recommends topical calcineurin inhibitors (tacrolimus and pimecrolimus) as third line treatment within their licensed indications to be used if

patients have not responded to the first line emollients and second line topical corticosteroids.

Neither tacrolimus nor pimecrolimus are considered first-line treatments due to historic concerns over lack of long-term safety data. Existing safety data from extended clinical trials indicates that the prevalence and range of adverse effects, notably systemic and skin infections, does not appear to be greater than that expected in the general population; current data is limited to a maximum of four years. Treatment with topical tacrolimus or topical pimecrolimus should only be initiated by prescribers experienced in treating atopic eczema.

More recently, tacrolimus ointment 0.03% and 0.1% (Protopic) have been licensed as maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare free intervals in patients experiencing a high frequency of disease exacerbations. PACEF reviewed a single trial comparing topical tacrolimus 0.1% ointment (on all affected body areas) and hydrocortisone acetate 1% ointment (head and neck) plus hydrocortisone butyrate 0.1% ointment (trunk and extremities) in adult patients with moderate to severe atopic dermatitis who were experiencing flares. Tacrolimus 0.1% ointment emerged as at least as effective as the corticosteroid regimen for the trunk and extremities and more effective in the face and neck area. However, there was a higher incidence of application site burning sensation associated with tacrolimus and a variety of infections reported including folliculitis and flu syndrome.

PACEF Recommendation:
Tacrolimus ointment 0.03% and 0.1% (Protopic) is designated AMBER without shared care for the treatment of moderate to severe atopic dermatitis in children aged over 2 years (0.03%) and adults and children aged over 16 years (0.1%) who have not adequately responded to or are intolerant of conventional therapies such as topical corticosteroids. Tacrolimus ointment 0.03% and 0.1% (Protopic) is also designated AMBER without shared care for the maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare free intervals in patients experiencing a high frequency of disease exacerbations. All topical tacrolimus therapy must only be initiated by prescribers experienced in treating atopic eczema only (i.e. dermatologists or GP with a special interest in dermatology).

NICE TECHNOLOGY APPRAISAL 241: *DASATINIB, HIGH-DOSE IMATINIB, AND NILOTINIB FOR THE TREATMENT OF IMATINIB-RESISTANT CHRONIC MYELOID LEUKAEMIA (CML) AND DASATINIB AND NILOTINIB FOR PEOPLE WITH CML FOR WHOM TREATMENT WITH IMATINIB HAS FAILED BECAUSE OF INTOLERANCE* (JANUARY 2012)

Key recommendations

Nilotinib is recommended for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults:

- whose CML is resistant to treatment with standard-dose imatinib **or**
- who have imatinib intolerance **and**
- if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.

Dasatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib.

High-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib.

People who are currently receiving dasatinib or high-dose imatinib for the treatment of CML should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

PACEF Recommendations:
Nilotinib capsules (Tasigna) are designated RED for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults. Dasatinib tablets (Sprycel) are designated RED-RED for the treatment of chronic, accelerated or blast-crisis phase CML in adults. High-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib. Imatinib tablets (Glivec) remain RED at standard-dose for the treatment of Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults.

NICE TECHNOLOGY APPRAISAL 242: *CETUXIMAB, BEVACIZUMAB AND PANITUMUMAB FOR THE TREATMENT OF METASTATIC COLORECTAL CANCER AFTER FIRST-LINE CHEMOTHERAPY* (JANUARY 2012)

Key recommendations

- Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.
- Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.
- Panitumumab monotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.
- People currently receiving cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin chemotherapy, or panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

PACEF Recommendation:
Cetuximab intravenous infusion (Erbitux) used as monotherapy or as combination chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. It is designated RED-RED for this indication. Cetuximab has been approved by NICE for other indications (e.g. locally advanced squamous cell cancer of the head and neck, metastatic colorectal cancer). Bevacizumab intravenous infusion (Avastin) in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. It is designated RED-RED for this indication. Panitumumab intravenous infusion (Vectibix) monotherapy is not recommended for the treatment of people with metastatic colorectal cancer

that has progressed after first-line chemotherapy. It is designated RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL 243: *RITUXIMAB FOR THE FIRST-LINE TREATMENT OF STAGE III-IV FOLLICULAR LYMPHOMA* (JANUARY 2012)

Key recommendation:

Rituximab, in combination with:

- cyclophosphamide, vincristine and prednisolone (CVP)
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
- mitoxantrone, chlorambucil and prednisolone (MCP)
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi) **or**
- chlorambucil

is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people.

PACEF Recommendation
Rituximab intravenous infusion (MabThera) in combination therapy is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people. Rituximab is designated RED for this indication.

NICE TECHNOLOGY APPRAISAL 244: *ROFLUMILAST FOR THE MANAGEMENT OF SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE* (JANUARY 2012)

Key recommendation:

Roflumilast is recommended only in the context of research as part of a clinical trial for adults with severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment.

People receiving roflumilast should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

PACEF Recommendation:
Roflumilast tablets 500 microgram (Daxas) are designated RED-RED for the treatment of severe COPD.

NICE TECHNOLOGY APPRAISAL 245: *APIXABAN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL HIP OR KNEE REPLACEMENT IN ADULTS* (JANUARY 2012)

Key recommendation

Apixaban is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery.

PACEF recommendation:
Apixaban 2.5mg tablets (Eliquis) are designated RED for the prophylaxis of venous thromboembolism in adults after hip or knee replacement surgery. Both rivaroxaban and dabigatran have also been approved by NICE for this indication and are also designated RED within this context. All three agents are in the process of being assessed by NICE, ULH Drug and Therapeutics Committee and PACEF for other licensed indications. None of these agents are currently approved for prescribing in primary care for any indication, although this is under review.

POLICY AND FORMULARY UPDATE

The following documents have been revised and updated and are now available:

- ***Wound Management Formulary*** **(5th Edition, March 2012)**
- ***Policy Relating to the Prescribing, Supply, Storage and Disposal of Controlled Drugs in Primary Care*** **(7th Edition, February 2012)**
- ***Lincolnshire Medication Procedure Guidance (Adult Care Homes)*** **(September 2011)**

All three of these documents are available through the PACEF section of the NHS Lincolnshire website.

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Stephen Gibson
Head of Prescribing and Medicines Management
NHS Lincolnshire

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