Greater East Midlands
Commissioning Support Unit

Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 7 **May 2013**

What's new this month?

- **The *Lincolnshire Joint Formulary* has now been published and is accessible on www.lincolnshirejointformulary.nhs.uk. This website is public facing and can be accessed by any patient wishing to determine whether a particular therapy is available in county (see page 3).**
- **Some prescribers have been experiencing difficulties accessing PACEF materials through the old NHS Lincolnshire website. Existing PACEF resources can still be accessed through www.lincolnshire.nhs.uk which has been re-launched as the *NHS in Lincolnshire* portal (see page 3).**
- **Prescribers are strongly advised not to pre-empt the launch of the national shingles vaccination programme by offering varicella zoster virus vaccine (*Zostavax*) on the NHS before the national programme is launched in September. Varicella zoster virus vaccine (*Zostavax*) is designated RED-RED and will continue to be classified as RED-RED even after the national programme launches; it should not be prescribed on NHS prescription, although appropriate patients can be prescribed for privately. Once the national programme has launched the vaccine will be available on the NHS to those in the target group (see page 4).**
- **All four of the Lincolnshire Clinical Commissioning Groups are in support of 28 day repeat prescribing as a means to minimise waste and ensure regular monitoring of patient compliance with therapy. PACEF have devised a statement to support this policy that can be used in consultation with patients resistant to idea. The statement will also be used to support responses to any patient complaints (see page 4).**
- **A national action plan entitled *Improving the use of medicines for better outcomes and reduced waste* has been published and provides a lot of ideas for CCGs, localities and individual practices to consider. These include: focusing on achieving better patient outcomes through improved adherance to therapy, improving repeat prescribing systems, better use of funded community pharmacy services such as repeat dispensing, medicines use reviews and the new medicines service, closer working between primary and secondary care to ensure use of patients own drugs in hospital and post-discharge and raising public awareness of pharmaceutical waste and ways to minimize it (see page 5).**
- **Hydrocortisone modified release 5mg and 20mg tablets (*Plenadren*) have been assessed and designated RED-RED (see page 7).**
- **Oxycodone prolonged release tablets (*Longtec*) are identical to *Oxycontin* in all key respects and are 20% less expensive. Prescribers are advised to prescribe**

all oxycodone prolonged release tablets 5mg, 10mg, 20mg, 40mg and 80mg as *Longtec.* Product switching is advocated wherever possible (see page 8).

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SUMMARY OF PACEF DECISIONS: *MARCH 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Argatroban infusion (*Exembrol*) 250mg/2.5ml	For use in adult patients with heparin-induced thrombocytopenia (HIT) type II who require parenteral antithrombotic therapy.	RED Approved for Joint Formulary
Denosumab injection (*Prolia*) 60mg	For the prevention of primary and secondary osteoporotic fragility fractures in post-menopausal women for whom bisphosphonates are unsuitable.	RED Further guidance is in development which may result in a revised classification. Approved for Joint Formulary for this indication. Long term use may be associated with atypical femoral fracture.
Denosumab injection (*XGEVA*) 120mg	For the prevention of skeletal-related events in adults with bone metastases from breast cancer and from solid tumours.	RED Further guidance is in development which may result in a revised classification. Approved for Joint Formulary for this indication. Long term use may be associated with atypical femoral fracture.
Denosumab injection (*XGEVA*) 120mg	For the prevention of skeletal-related events in adults with bone metastases from prostate cancer.	RED-RED Not approved for Joint Formulary for this indication. Long term use may be associated with atypical femoral fracture.
Efavirenz, emtricitabine and tenofovir disoproxil tablets (*Atripla*)	For the treatment of HIV-1 infection	RED
Fingolimod 500microgram capsules (*Gilenya*)	For the treatment of highly active relapsing–remitting multiple sclerosis (MS) in patients whose disease has failed to respond to beta-interferon or is severe and getting rapidly worse.	RED Further guidance is in development which may result in a revised classification. Approved for Joint Formulary for this indication.
Hydrocortisone modified release 5mg and 20mg tablets (*Plenadren*)	For maintenance therapy in adrenal insufficiency	RED-RED Not approved for Joint Formulary

Lenalidomide 5mg, 10mg, 15mg, 25mg capsules (*Revlimid*)	Used in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy.	RED Approved for Joint Formulary for this indication.
Oxycodone prolonged release tablets 5mg, 10mg, 20mg, 40mg and 80mg (*Longtec*)	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.	GREEN Product switching from *Oxycontin* to *Longtec* now advocated. Already approved for Joint Formulary
Roflumilast 500 microgram tablets (*Daxas*)	For the maintenance treatment of severe chronic obstructive pulmonary disease associated with chronic bronchitis.	RED-RED Not approved for Joint Formulary
Varicella zoster virus vaccine (*Zostavax*)	For the prevention of shingles and post-herpetic neuralgia in adults aged 50 years and older	RED-RED Not approved for Joint Formulary. A national vaccination programme for adults aged 70 and 79 is due to be rolled out from September 2013.

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 in Lincolnshire website (www.lincolnshire.nhs.uk). Follow the commissioning'link to PACEF.

JOINT FORMULARY NOW PUBLISHED

The First Edition of the *Lincolnshire Joint Formulary* is now complete and is accessible through its own website www.lincolnshirejointformulary.nhs.uk All prescribers are encouraged to visit the site and to familiarise themselves with the content. Any comments and suggestions for subsequent editions would be welcomed. This website is public facing and can be accessed by any patient wishing to determine whether a particular therapy is available in county. The Joint Formulary Group will now begin the task of refining the document to make it even more useful. A primary care version is planned and the existing version is to be supplemented with contextual information on the use of each medicine. There are also plans to make reference to products that should not be prescribed so that a search of the document will provide information on both formulary and non-formulary products.

ACCESSING PACEF INFORMATION THROUGH THE *NHS IN LINCOLNSHIRE* WEBSITE

Some prescribers have been experiencing difficulties accessing PACEF materials through the old NHS Lincolnshire website. Existing PACEF resources can still be accessed through www.lincolnshire.nhs.uk which has been re-launched as the *NHS in Lincolnshire* portal. However, the full internet address (URL) of the PACEF section of the site has changed from:

www.lincolnshire.nhs.uk/en/commissioning/pacef to
http://www.lincolnshire.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef

Some prescribers using a favourite/bookmark to get directly to the PACEF section of the old NHS Lincolnshire website have been receiving an error message saying "file / directory not found". Anyone experiencing this problem should access the *NHS in Lincolnshire* home page (www.lincolnshire.nhs.uk) and then follow the commissioning link to PACEF. A new

bookmark can then be created or this process can be followed each time the site is accessed.

CHANGES TO NATIONAL IMMUNISATION PROGRAMME IN 2013-14: HERPES ZOSTER VACCINE

A letter from the Department of Health, Public Health England and NHS England issued on April 30th 2013 has detailed changes to the national immunisation programme in response to recommendations made by the Joint Committee on Vaccination and Immunisation (JCVI). Specifically, from September 2013, herpes zoster (or shingles) vaccine will be phased in for people in their 70s. Initially, those aged 70 and 79 years will be invited to take up the vaccination with the programme expanding to incorporate more of the 70 to 79 age group over the next few years. Approximately 800,000 people will be eligible to receive the vaccine in the first year. Elderly people are at greatest risk of shingles; it is envisaged that vaccination will prevent nearly half of cases of shingles in the over 70s amounting to tens of thousands of cases prevented every year.

PACEF Recommendation

Prescribers are strongly advised not to pre-empt the launch of the national shingles vaccination programme by offering varicella zoster virus vaccine (*Zostavax*) on the NHS before the national programme is launched in September. Varicella zoster virus vaccine (*Zostavax*) is designated RED-RED and will continue to be classified as RED-RED even after the national programme launches; it should not be prescribed on NHS prescription, although appropriate patients can be prescribed for privately. Once the national programme has launched the vaccine will be available on the NHS to those in the target group. *Zostavax* is licensed for the prevention of shingles and post-herpetic neuralgia in adults aged 50 years and older; even after the launch of the national campaign, it is recommended that patients aged between 50 and 69 should only receive the vaccine on private prescription.

Other changes to the national immunisation programme reported in the DoH/PHE/NHS England letter of 30th April include:

- An extension to the existing flu immunisation programme phased-in over a number of years to include all children aged 2 to 16 inclusive.
- The introduction into the childhood immunisation schedule of a vaccine to protect babies against rotavirus.
- Changes to the current schedule for administering the Meningitis C conjugate vaccine. The second priming dose currently given at 4 months will be replaced by a booster dose given in adolescence.

LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS: *STATEMENT IN SUPPORT OF 28 DAY PRESCRIBING*

One of the most common sources of patient complaint relating to prescribing arises from frustration with the standard 28 day repeat prescribing interval preferred by most practices and endorsed historically by NHS Lincolnshire. Typically, a younger patient with a long-term condition managed with a single therapy and subject to prescription charges will challenge the need for monthly repeats and request a longer prescribing interval of two to three months. Many published audits, studies and reports, culminating in the York Health Economics Consortium report in 2010, have endorsed 28 day prescribing as the best way to minimise waste and ensure regular monitoring of patient compliance with therapy,

particularly where multi-component prescriptions are synchronised to a single monthly request. In order to support those practices who find their 28 day prescribing policy challenged by one or more of their patients, PACEF has developed the following statement on behalf of all four of the Lincolnshire Clinical Commissioning Groups and Lincolnshire Community Health Services. This statement can be used in practice to justify practice policy; it will also be used in response to any patient complaints:

> In general, Lincolnshire Clinical Commissioning Groups and Lincolnshire Community Health Services support GP practices and prescribers who wish to issue regular monthly repeat prescriptions to their patients rather than larger quantities. We believe that there are many advantages to doing this including the potential for reduction in pharmaceutical waste and the prospect of close monthly monitoring of the patients repeat ordering pattern to ensure, as far as possible, good compliance with therapy. There are also instances in which the law specifically forbids the issue of larger quantities of particular medicines. For example, the Department of Health advise that Controlled Drugs (Schedules 2, 3 and 4) should be prescribed for no longer than intervals of 30 days unless exceptional circumstances prevail.
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> A number of mechanisms are available to support patients who are taking regular medication:
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> Remote Ordering of Repeat Prescriptions
> Many GP Surgeries are equipped to register patients to facilitate ordering of their repeat prescription online or over the telephone.
> Collection and Delivery Services
> Contact your GP Surgery or regular Community Pharmacy for more details of availability of these services.
> Pre-Payment Certificates (PPC)
> PPCs may provide a way to reduce the cost of monthly repeat medications. A PPC presents a potentially lower cost option for patients who have to pay for more than 3 prescriptions in 3 months or more than 13 items in 12 months. More information is available from your GP Surgery, Community Pharmacy or from the NHS Business Service Authority telephone advice and order line, telephone 0845 850 0030 or online at www.nhsbsa.nhs.uk under "*Help with Heath Cost.*
>
> In individual exceptional circumstances, where the prescriber has no clinical concerns, larger quantities than 28 days may be issued on repeat prescription. This is within the discretion of the GP Surgery and the individual prescriber. Patients are advised to discuss their individual situation with their GP. Many practices will issue prescriptions for larger quantities of oral contraceptives and hormone replacement therapy due to larger pack sizes. Recent guidance from the MHRA has also advocated prescribing of 3 month quantities of levothyroxine tablets.

***IMPROVING THE USE OF MEDICINES FOR BETTER OUTCOMES AND REDUCED WASTE:* AN ACTION PLAN OF THE NATIONAL STEERING GROUP ON IMPROVING THE USE OF MEDICINES (OCTOBER 2012)**

In November 2010, the York Health Economics Consortium and The School of Pharmacy, University of London published *Evaluation of the Scale, Causes and Costs of Waste Medicines.* A subsequent national Steering Group on Improving the Use of Medicines convened in September 2011 and has just published an action plan designed to implement

many of the findings of the York Report, reduce the scale of medicines waste and improve patient outcomes through better use of medicines. Key learning points for practices, localities and CCGs are as follows:

- Minimising medicines waste entails: (1) reducing the amount of medicines sent for incineration; (2) improving repeat prescribing and dispensing systems; (3) ensuring that prescribing is rational and cost-effective and (4) ensuring that patients take their medicines as intended.
- The York Report (November 2010) suggests that improving the use of medicines in 5 therapeutic areas could potentially save £500M pa through improved outcomes; these therapeutic areas are statins, hypertension, type 2 diabetes, asthma and schizophrenia. Increased focus on improving patient adherence in these therapy areas could reap significant benefits in terms of both improving patient care and reducing waste.
- Inadequately managed repeat prescribing and lack of formal review increases the risk of medicines waste and can put patient safety at risk. Practices need to ensure that best practice repeat prescribing guidance is in place to minimise problems. The GEM Prescribing and Medicines Optimisation Team can provide support to practices, localities and CCGs where this is identified as an issue.
- Repeat dispensing is a service funded under the community pharmacy contract whereby GPs can print out up to 12 prescriptions at once to be dispensed at appropriate intervals by a community pharmacist (up to 12 months of treatment). Allowing the community pharmacist to manage repeat requests reduces demands on the practice and enables the pharmacist to become more involved in monitoring patient compliance and identifying emerging problems. Many of the initial teething problems associated with repeat dispensing as a paper-based system are likely to be resolved by the impending roll-out of Electronic Prescribing Service 2 (EPS2). Participation in repeat dispensing measured in terms of percentage of scripts dispensed through this system may become a national QIPP comparator with CCGs benchmarked against peers. At present, participation in repeat dispensing services in Lincolnshire is relatively low as illustrated by the following table:

	Repeat dispensing rate (%)
Lincolnshire East CCG	0.13%
SW Lincolnshire CCG	3.22%
South Lincolnshire CCG	0.47%
Lincolnshire West CCG	3.12%
Lincolnshire	1.49%
National	5.64%

- CCGs and practices also need to consider whether they are maximising the benefit of already funded community pharmacy services including Medicines Use Reviews (MURs) and the New Medicines Service (NMS). Closer working between individual practices and community pharmacies could help to develop shared agendas around review of particular groups of patients (e.g. those with multiple, complex long term conditions), particular medicines or particular disease areas.
- CCGs and local Acute Trusts need to work together to be mutually supportive of initiatives taken on either or both sides of the interface to minimise waste. Specifically, local Acute Trusts are encouraging patients to take all of their medicines with them when they go into hospital to maximise their use of Patients' Own Drugs (PODs) during their in-patient stay.
- CCGs or localities may wish to raise the profile of medicines waste through local publicity campaigns. Key messages include: (1) Reducing waste is everyone's business; (2) The NHS is a precious resource; use it wisely; (3) 'It's OK to ask about medicines'; (4) It's OK

to inform your GP, nurse or pharmacist is you are experiencing problems with your medicines or if taking them does not fit into your daily activities; (5) 'Stop the stockpile'; (6) Dispose of medicines safely. Take them to your local community pharmacy or dispensing practice. Do not throw them into the domestic waste or flush down the toilet; (7) If you are going into hospital, take your medicines with you for use during your stay. They will be returned to you on discharge, if you still need them; (8) Only order what you need.

NEW DRUG ASSESSMENT: HYDROCORTISONE MODIFIED RELEASE 5MG AND 20MG TABLETS (*PLENADREN*)

Plenadren is a new hydrocortisone modified release formulation available as both 5mg and 20mg tablets and licensed for the treatment of adults with adrenal insufficiency. A single small randomised cross over study was reviewed that compared once daily *Plenadren* with immediate release hydrocortisone taken three times a day (the more usual UK dose regimen is twice daily). The two treatment approaches were compared by measuring total serum cortisol area under the curve over a 24 hour period – the so-called serum cortisol exposure time profile. Monitoring revealed that *Plenadren* produced a high peak of serum cortisol after the morning dose and then a slow decline during the afternoon with negligible levels overnight; this only partly mimics the natural cortisol release pattern which also includes a gradual rise in cortisol levels just before wakening and two day time spikes associated with eating. The trial also demonstrated that the amount of hydrocortisone absorbed systemically from *Plenadren* is about 20% less milligram for milligram than that absorbed with immediate release hydrocortisone. This may help to reduce the risk of over-substitution and associated weight gain, but also carries the risk of under-substitution in some. Data from one supporting trial indicated that fatigue was more frequently reported with those taking *Plenadren* compared to immediate release hydrocortisone, particularly within the first eight weeks of treatment. This may be reflective of under-substitution in some patients. Secondary outcomes from the small cross over study show improved metabolic outcomes, such as reduction in blood pressure, weight, body mass index and HbA1c, with *Plenadren*, although this could simply be a function of under-substitution. There is also no trial data comparing *Plenadren* with other alternatives such as prednisolone or dexamethasone.

A cost comparison reveals the following:

Treatment	Dose	Cost of 28 days treatment
Hydrocortisone MR tablets 20mg tablets (*Plenadren*)	20mg daily	£224.00
Hydrocortisone immediate release tablets	10mg morning, 5mg afternoon and evening	£87.42

Over a year, *Plenadren* costs an additional £1,775.54 per patient more than standard hydrocortisone treatment.

PACEF Recommendation:
Existing trial data comparing hydrocortisone MR 20mg tablets (*Plenadren*) with immediate release hydrocortisone tablets is limited, short-term and inconclusive. In addition, *Plenadren* is significantly more expensive than conventional immediate release hydrocortisone. As a result of this, hydrocortisone MR tablets 20mg tablets (*Plenadren*) are designated RED-RED and should not be prescribed in either secondary or primary care.

NEW DRUG ASSESSMENT: ARGATROBAN INFUSION (*EXEMBROL*)

Argatroban infusion (*Exembrol*) is licensed in adult patients with heparin-induced thrombocytopenia (HIT) type II who require parenteral antithrombotic therapy. In two similarly-designed, open-label, non-randomised, historically-controlled trials in adult patients with HIT, argatroban demonstrated a prompt anticoagulant effect. It is currently the only licensed treatment option that can be used in patients with renal impairment (frequently a complication of HIT). The cost per patient is dependent on the rate of infusion required and ranges between £1789.20 and £7753.20.

PACEF Recommendation:
Following a favourable assessment of this product by ULH Drug and Therapeutics Committee, PACEF approved argatroban infusion (*Exembrol*) for use in adult patients with heparin-induced thrombocytopenia (HIT) type II. Designation: RED.

RAPID DRUG ASSESSMENT: EFAVIRENZ, EMTRICITABINE AND TENOFOVIR TABLETS (*ATRIPLA*)

Atripla is a fixed dose combination antiretroviral licensed for the treatment of HIV infection. It contains efavirenz, emtricitabine and tenofovir disoproxil which are all recommended as options for the treatment of HIV-1 positive adults by the British HIV Association guideline. This guideline also states that fixed dose combinations products may have a role in improving adherence to therapy in HIV, although clinicians need to take into account other factors such as effectiveness, tolerability and resistance profiles. *Atripla* is less costly as a combination than the individual components prescribed separately at the same doses.

PACEF Recommendation:
On the basis that *Atripla* provides a combination of British HIV Association approved antiretroviral drugs at a price that is lower than the components prescribed separately, *Atripla* tablets are designated RED.

RAPID REVIEW: *OXYCODONE PROLONGED RELEASE TABLETS (LONGTEC)*

This is an updated version of a new product assessment that originally appeared in *PACE Bulletin* Vol 6 No 19 (December 2012)

Longtec is the brand name for a generic prolonged release range of oxycodone tablets recently launched by Qdem Pharmaceuticals Ltd. The product is manufactured under license from the manufacturer of the originator brand, *Oxycontin* (Napp). Qdem have launched *Longtec* in five strengths, 5mg, 10mg, 20mg, 40mg and 80mg, all of which appear identical in shape and colour to *Oxycontin*, have identical blister packaging and are even manufactured in the same factory. *Oxycontin* is available in a wider range of strengths, but is 20% more expensive than *Longtec* (see cost comparison below):

Drug	Dose	Cost
Oxycodone prolonged release tablets 5mg (*Longtec*)	**5mg every 12 hours**	**£20.00 (2x28's)**
Oxycodone prolonged release tablets 10mg (*Longtec*)	**10mg every 12 hours**	**£19.99**
Oxycodone prolonged release tablets 20mg (*Longtec*)	**20mg every 12 hours**	**£39.98**

Oxycodone prolonged release tablets 40mg (*Longtec*)	**40mg every 12 hours**	**£79.98**
Oxycodone prolonged release tablets 80mg (*Longtec*)	**80mg every 12 hours**	**£159.98**
Oxycodone prolonged release tablets 5mg (*Oxycontin*)	5mg every 12 hours	£25.00
Oxycodone prolonged release tablets 10mg (*Oxycontin*)	10mg every 12 hours	£24.99
Oxycodone prolonged release tablets 15mg (*Oxycontin*)	15mg every 12 hours	£37.41
Oxycodone prolonged release tablets 20mg (*Oxycontin*)	20mg every 12 hours	£49.98
Oxycodone prolonged release tablets 30mg (*Oxycontin*)	30mg every 12 hours	£74.81
Oxycodone prolonged release tablets 40mg (*Oxycontin*)	40mg every 12 hours	£99.98
Oxycodone prolonged release tablets 60mg (*Oxycontin*)	60mg every 12 hours	£149.66
Oxycodone prolonged release tablets 80mg (*Oxycontin*)	80mg every 12 hours	£199.97
Oxycodone prolonged release tablets 120mg (*Oxycontin*)	120mg every 12 hours	£299.31

Ref: *MIMS* March 2013

Undeniably, *Longtec* is available in fewer strengths than *Oxycontin*, although the most widely prescribed strengths of *Oxycontin* are available in the *Longtec* range.

PACEF Recommendation:
PACEF reviewed oxycodone prolonged release tablets (*Longtec*) in October 2012 and the product was designated GREEN. *Longtec* tablets are identical to *Oxycontin* in all key respects and are 20% less expensive. Prescribers are advised to prescribe all oxycodone prolonged release tablets 5mg, 10mg, 20mg, 40mg and 80mg as *Longtec.* Product switching is advocated wherever possible. It is acknowledged that *Oxycontin* is available in a wider range of strengths and will continue to be necessary for a minority of patients.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) *DRUG SAFETY UPDATE* (January 2013)

Fingolimod (*Gilenya*): bradycardia and heart block – repeat cardiovascular monitoring when restarting fingolimod after treatment interruption.

Fingolimod (*Gilenya*) is licensed for the treatment of relapsing–remitting multiple sclerosis (MS) in patients whose disease has failed to respond to beta-interferon or is severe and getting rapidly worse. Safety concerns were first raised by the MHRA in February 2012. Fingolimod is known to cause transient bradycardia and heart block after the first dose. A subsequent *Drug Safety Update* published in May 2012 provided further details on the level of monitoring required. Further information has now emerged raising concern that the effects of fingolimod on heart rate and atrio-ventricular conduction may recur on reintroduction of the treatment following interruption. The MHRA are now advising that if treatment is stopped for more than two weeks for any reason, the patient should be monitored in the same way as those starting treatment. Those patients who required pharmacological treatment for symptoms of bradycardia on day 1 will also require the same level of monitoring on day 2.

The MHRA have also issued advice to patients as follows:

- If you have been taking *Gilenya* for less than one month and you forget to take 1 dose for a whole day call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose.
- If you have been taking *Gilenya* for at least a month and have forgotten to take your treatment for more than 2 weeks, call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose. However of you have forgotten to take your treatment for up to 2 weeks, you can take the next dose as planned.
- Never take a double dose to make up for a forgotten dose.

PACEF Comment:
PACEF recently reviewed NICE TA 254 in which fingolimod (*Gilenya*) was approved as an option for the treatment of highly active and relapsing MS. Designation: RED. There should be no current prescribing of fingolimod in Lincolnshire primary care At present all prescribing, administration and monitoring of fingolimod therapy is the responsibility of specialist services.

Lenalidomide (*Revlimid*) risk of serious hepatic adverse drug reactions – routine monitoring of liver function now recommended

Lenalidomide (*Revlimid*) is used in combination with dexamethasone for the treatment of multiple myeloma. Reports suggest that lenalidomide may be associated with drug-induced injuries, although the number of cases is small. Pre-disposing factors to lenalidomide induced injury include: elevated baseline liver enzymes, pre-existing viral liver disease, concomitant treatment with known hepatotoxic medicines and older age.

The MHRA have issued the following advice to healthcare professionals:

- Routine monitoring of liver function is required for patients receiving lenalidomide, particularly in those with predisposing risk factors (see above).
- Prescribers should consider the possibility of lenalidomide induced liver injury in patients presenting with otherwise unexplained deterioration of liver function.
- Impairment of liver function generally resolves when lenalidomide treatment is stopped. Once abnormal liver function parameters return to baseline values, treatment can be restarted at a lower dose if required.
- Lenalidomide is renally excreted. It is important to adjust the dose if the patient is renally impaired to avoid excessive plasma levels which may increase the risk of hepatoxicity as well as haematological adverse effects.

PACEF Comment
Lenalidomide capsules (*Revlimid*) are approved for use in combination with dexamethasone for the treatment of multiple myeloma. Designation: RED. At present, there is no GP prescribing within Lincolnshire primary care. All monitoring associated with this treatment is usually the responsibility of the hospital based specialist service.

Roflumilast (*Daxas*) risk of suicidal behaviour – avoid use in patients with previous or existing psychiatric symptoms and discontinue treatment if new or worsening symptoms are identified

A recent post marketing report on roflumilast (*Daxas*) has identified cases of suicidal behaviour in patients both with and without a history of depression, usually within the first weeks of treatment. The MHRA have issued the following advice to healthcare professionals:

- Roflumilast is not recommended for patients with a history of depression associated with suicidal ideation or behaviour.
- Patients and care givers should be asked to notify the prescriber and their healthcare provider of any changes to behaviour or mood and any suicidal ideation. Such symptoms include preoccupation with suicidal thoughts and self-harm.
- Roflumilast should be discontinued if new or worsening psychiatric symptoms or suicidal behaviour are identified.

PACEF recommendation

Roflumilast (*Daxas*) is licensed for the maintenance treatment of severe chronic obstructive pulmonary disease associated with chronic bronchitis. It was assessed by NICE in TA 244 (January 2012) and recommended for use only within the context of research. People currently receiving the treatment had the option to continue until they or their clinician considered it appropriate to stop. On this basis there remain a small number of patients in Lincolnshire continuing to receive this therapy on GP prescription. On the basis of NICE advice, roflumilast (*Daxas*) has been designated RED-RED for this indication. Prescribers are urged to review any patients that are still receiving roflumilast on prescription according to MHRA criteria.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)
***DRUG SAFETY UPDATE* (February 2013)**

Denosumab 60mg (*Prolia*): rare cases of atypical femoral fracture with long term use

Atypical femoral fractures have been reported in two patients with post-menopausal osteoporosis receiving long term treatment (≥2.5 years) with denosumab 60mg given once every 6 months as part of the FREEDOM trial. The nature of these fractures is similar to that seen with long-term bisphosphonate therapy. Although reported in association with the 60mg dose of denosumab (*Prolia*), a risk of atypical femoral fracture with the higher dose of 120mg marketed as *Xgeva* cannot be excluded. *Xgeva* is administered once every 4 weeks for the prevention of skeletal events in adults with bone metastases from solid tumours.

The MHRA have issued the following advice to healthcare professionals:

- During treatment, patients should be advised to report new or unusual thigh, hip or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.
- Atypical femoral fractures may occur with little or no trauma in the sub trochanteric and diaphyseal regions of the femur.
- The contralateral femur should be examined in denosumab treated patients who have sustained a femoral shaft fracture as atypical femoral fractures are often bilateral.
- Discontinuation of denosumab treatment should be considered if an atypical femoral fracture is suspected. While the patient is evaluated an individual risk assessment of the risk-benefits should be performed.

PACEF Comment

PACEF previously approved denosumab 60mg injection (*Prolia*) for the prevention of primary and secondary osteoporotic fragility fractures in post-menopausal women for whom bisphosphonates are unsuitable. Designation: RED. Similarly, denosumab 120mg (*Xgeva*) was approved for the prevention of skeletal-related events in adults with bone metastases from breast cancer and from solid tumours following approval by NICE in TA 265. Designation: RED. At present all prescribing, administration and monitoring of denosumab therapy remains the responsibility of specialist services. GPs should be aware of the potential risk of atypical femoral fractures associated with denosumab as patients currently receiving treatment may first present in primary care for advice and help.

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