Greater East Midlands Commissioning Support Unit

Greater East Midlands Commissioning Support Unit in association with
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,
United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 18 **October 2013**

What's new this month?

- **In response to MHRA advice, ketoconazole 200mg tablets (*Nizoral*) are designated RED-RED for the treatment of fungal infections and have been removed from the *Joint Formulary* for this indication. This is due to the increased risk of liver injury including hepatitis, cirrhosis and liver failure. Prescribers are urged to review any remaining patients currently receiving oral ketoconazole with a view to stopping treatment or using an alternative. Oral ketoconazole should not be initiated in new patients for this indication. Off label use for patients with Cushing's syndrome may still be appropriate subject to continuing product availability (see page 3).**
- **The European Committee on Medicinal Products for Human Use (CHMP) has undertaken a safety review of metoclopramide and confirmed the already well documented risk of neurological effects, such as short-term extrapyramidal disorders and tardive dyskinesia; these risks are increased at high doses or with long-term treatment. In response to this the MHRA have issued guidance on maximum doses in both adults and children and have recommended that metoclopramide should only be prescribed for short periods (up to 5 days). Since the publication of this advice, one of the manufacturers has requested a re-examination of the evidence and publication of the final outcome is still pending. In the meantime, prescribers are advised to be mindful of the maximum doses in adults and children and to avoid long-term use where possible. Further guidance will be published once the CHMP complete their final review (see page 3).**
- **A large-scale trial designed to fully investigate the safety concerns around the use of the tiotropium *Spiriva Respimat* inhaler has concluded that the device is as safe as the tiotropium *HandiHaler* in terms of both risk of death and risk of first COPD exacerbation. As a result of this, tiotropium (*Spiriva Respimat*) 2.5 microgram per dose has been reclassified from RED-RED to GREEN; the tiotropium *Spiriva HandiHaler* is already designated GREEN (see page 5).**
- **Where a salbutamol MDI is used in conjunction with a spacer device the required dose should be administered by repeated single aspirations into the spacer followed by inhalation, rather than by multiple actuations into the spacer. Evidence suggests that administering each dose separately increases the amount of drug available for inhalation by over 20% (see page 8).**

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SUMMARY OF PACEF DECISIONS: *SEPTEMBER 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Aflibercept solution for injection (*Eylea*)	For neovascular (wet) age-related macular degeneration.	RED Approved for inclusion in the *Joint Formulary.*
Ketoconazole 200mg tablets (*Nizoral*)	For the treatment of fungal infections	RED-RED Removed from the *Joint Formulary* for this indication.
Oxybutynin 2.5mg in 5ml elixir (*Ditropan Elixir*).	For the treatment of urinary frequency, urgency, urge incontinence and neurogenic bladder disorders; also nocturnal enuresis in children.	GREEN Approved for inclusion in the *Joint Formulary*
Pegloticase infusion 8mg (*Krystexxa*)	For the treatment of severe debilitating chronic tophaceous gout in adults who may also have erosive joint involvement and in whom xanthine oxidase inhibitors at the maximum medically appropriate dose have failed to normalise serum uric acid, or for whom these medicines are contraindicated.	RED-RED Not approved for inclusion in the *Joint Formulary*.
Ruxolitinib 15mg and 20mg tablets (*Jakavi*)	For the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.	RED-RED Not approved for inclusion in the *Joint Formulary*.
Tiotropium (*Spiriva HandiHaler)* 18 microgram per dose	For the maintenance treatment of chronic obstructive pulmonary disease	GREEN Already included in the *Joint Formulary.*
Tiotropium (*Spiriva Respimat)* 2.5 microgram per dose	For the maintenance treatment of chronic obstructive pulmonary disease	GREEN Approved for reintroduction into the *Joint Formulary*

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. Electronic copies of both the *PACE Bulletin* and our sister publication *PACE Shorts* (a short summary of the *PACE Bulletin*) are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk

PRODUCT RELAUNCH: *OXYBUTYNIN 2.5MG IN 5ML ELIXIR (DITROPAN ELIXIR)*

The anticholinergic agent oxybutynin has been re-launched as a 2.5mg in 5ml elixir (*Ditropan Elixir*). The product is authorized to treat urinary frequency, urgency, urge incontinence and neurogenic bladder disorders; also nocturnal enuresis in children. *Ditropan Elixir* is the only authorized liquid formulation of oxybutynin available in the UK. At a cost of £6.88 for 150ml, a months' supply of *Ditropan Elixir* can cost anything from £13.76 to £55.04 depending on the dose.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (AUGUST 2013)

ORAL KETOCONAZOLE – RISK OF LIVER INJURY OUTWEIGHS BENEFITS

The European Medicines Agency Committee on Medicinal Products for Human Use (CHMP) has evaluated the risk of liver injury (such as hepatitis, cirrhosis and liver failure) associated with ketoconazole. The onset of hepatotoxicity occurred generally between 1 and 6 months after starting treatment, but has been reported earlier than this and at the recommended daily dose of 200 mg.

Taking into account the increased rate of liver injury and the availability of alternative antifungal treatments, the CHMP have concluded that the benefits of ketoconazole therapy did not outweigh the risks. MHRA advice for healthcare professionals is as follows:

- **Oral ketoconazole should not be prescribed for fungal infections.**
- Doctors should review patients with a view to stopping treatment or using an alternative therapy.
- Pharmacist should refer patients with prescriptions for ketoconazole for fungal infections to their GP for a non-urgent appointment to discuss an alternative.
- Topical ketoconazole formulations have a very low systemic absorption and may continue to be used.
- Ketoconazole is sometimes used off label for patients with Cushing's syndrome. Arrangements will need to be put in place to ensure these patients continue to have access to oral ketoconazole for off label indications.

PACEF Recommendation:
In response to MHRA advice, ketoconazole 200mg tablets (*Nizoral*) are designated RED-RED for the treatment of fungal infections and have been removed from the *Joint Formulary* for this indication. EPACT analysis of primary care prescribing data has revealed that oral ketoconazole 200mg tablets are still prescribed, albeit infrequently, in all four of the Lincolnshire CCGs. Prescribers are urged to review any remaining patients currently prescribed oral ketoconazole with a view to stopping treatment or using an alternative. Oral ketoconazole should not be initiated in new patients for this indication. Off label use for patients with Cushing's syndrome may still be appropriate subject to continuing product availability.

METOCLOPRAMIDE – RISK OF NEUROLOGICAL ADVERSE EFFECTS

The EMA Committee on Medicinal Products for Human Use has reviewed the risk and benefits of metoclopramide. This was carried out at the request of the French medicines regulatory agency (ANSM) in response to continuing concerns over efficacy and safety.

The review confirmed the already well-known risk of neurological effects, such as short-term extrapyramidal disorders (involuntary movements often involving the head and neck), and tardive dyskinesia (uncontrollable movements such as grimacing and twitching). The risk of

short-term neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly; these risks are increased at high doses or with long-term treatment. **The review concluded that the risk of metoclopramide therapy outweighed the benefit in conditions requiring high-dose or long-term treatment.** Very rare cases of serious effects on the heart or circulation, particularly after injection, were also identified as part of the review.

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In response to this review, the MHRA have issued the following advice:

- In adults, metoclopramide remains indicated for the prevention of postoperative nausea and vomiting; radiotherapy- induced nausea and vomiting; delayed (but not acute) chemotherapy-induced nausea and vomiting; and symptomatic treatment and nausea and vomiting, including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics).
- In children aged 1-18 years, metoclopramide should only be used as a second-line option for the prevention of delayed chemotherapy-induced nausea and vomiting and for the treatment of established postoperative nausea and vomiting.
- The use of metoclopramide is contraindicated in children younger than 1 year.
- Metoclopramide should only be prescribed for short-term use (up to 5 days).
- In adults, the maximum dose in 24 hours is 30mg (usual dose 10mg three times daily) or 0.5mg per kg bodyweight.
- In children aged 1 year or older, the recommended dose is 0.1 to 0.15mg per kg bodyweight, repeated up to three times day. The maximum dose in 24 hours is 0.5mg per kg bodyweight.
- Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy in children.

PACEF Recommendation:

The European CHMP review confirms the already well documented risk of neurological effects with metoclopramide, such as short-term extrapyramidal disorders and tardive dyskinesia; these risks are increased at high doses or with long-term treatment. In response to this, the MHRA have issued guidance on maximum doses in both adults and children and have recommended that metoclopramide should only be prescribed for short periods (up to 5 days).Since the publication of this advice, one of the manufacturers has requested a re-examination of the evidence and publication of the final outcome is still pending. As a result of this, PACEF have decided to publicize the MHRA position on metoclopramide as detailed above but to refrain from publishing local guidance on implementation until the European CHMP have completed their review. Prescribers are advised to be mindful of the maximum doses in adults and children and to avoid long-term use where possible. PACEF are aware that metoclopramide is widely prescribed across NHS primary care. In Lincolnshire alone, 24,000 prescriptions for metoclopramide are issued every year and implementation of this guidance as it currently stands is likely to have major implications for both clinicians and patients. Further guidance will be published once the CHMP complete their final review.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (SEPTEMBER 2013)

FILGRASTIM AND PEGFILGRASTIM – RISK OF POTENTIALLY LIFE THREATENING CAPILLARY LEAK SYNDROME

Capillary Leak Syndrome (CLS) has been reported in recipients of filgrastim, including patients undergoing chemotherapy and in a healthy donor undergoing peripheral blood

progenitor cell mobilisation. CLS has also been reported in recipients of pegfilgrastim undergoing chemotherapy.

CLS is characterised by hypotension, oedema, hypoalbuminaemia and haemoconcentration and may be fatal unless promptly diagnosed and managed. Symptoms experienced by patients will be generalised body swelling, puffiness (which may be associated with less frequent urination), difficulty in breathing, abdominal swelling and tiredness. Prescribers should monitor patients and healthy donors for signs and symptoms of CLS and give standard symptomatic treatment if symptoms occur. Patients should be advised to seek urgent medical attention if they experience any of these symptoms.

PACEF Comment:
Both filgrastim injection (*Neupogen*/*Nivestim*/*Ratiograstim*/*Tevagrastim*/*Zarzio*) and pegfilgrastim injection (*Neulasta*) are designated as RED for all indications and should only be prescribed and administered as part of a specialist service provided from within secondary or tertiary care. Primary care prescribers managing the general medical needs of these patients need to be aware of the risk of CLS documented above.

NEW TRIAL ASSESSMENTS

TIOTROPIUM *SPIRIVA RESPIMAT* INHALER AND THE RISK OF DEATH IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In this randomized controlled trial (RCT) involving 17,135 patients, the tiotropium *Respimat* device at a once daily dose of 2.5 microgram and 5 microgram was compared with the tiotropium *HandiHaler* at a dose of 18 microgram a day. The primary end points were risk of death and risk of first COPD exacerbation. During a mean follow-up of 2.3 years Respimat was found to be non-inferior to *HandiHaler* with respect to risk of death and not superior to *HandiHaler* with respect to risk of first COPD exacerbation. Causes of death and incidences of major cardiovascular disease were similar in the *Respimat* and *HandiHaler* groups.

PACEF Comment:
PACEF previously reviewed the safety of the tiotropium *Spiriva Respimat* device after a pooled analysis of 3 trials and a placebo controlled trial showed an association between *Respimat* use and excess mortality and cardiovascular death, particularly in patients with a history of cardiac arrhythmias. This contrasted with the findings of studies using tiotropium *Handihaler* which had been shown to be associated with a reduction in all-cause mortality compared to placebo. Subsequent meta-analyses of data failed to resolve this issue. This large-scale trial was designed to fully investigate these concerns and was sufficiently powered to estimate a mortality difference between the two devices. After reviewing this data, PACEF are satisfied that any safety concerns related to the use of the *Respimat* device have been sufficiently investigated and resolved. As a result of this, tiotropium (*Spiriva Respimat*) 2.5 microgram per dose has been reclassified from RED-RED to GREEN; the tiotropium *Spiriva HandiHaler* is already designated GREEN. Both products will now be included in the *Joint Formulary.*

Reference
Wise RA et al., Tiotropium *Respimat* Inhaler and the risk of death in COPD. *N Engl J Med* 2013; DOI:10.1056/NEJMoa1303342

SAXAGLIPTIN AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

In this RCT, 16,492 people with type 2 diabetes and cardiovascular disease or with multiple risk factors for CV disease were randomised to receive saxagliptin or placebo, in addition to other diabetic medication determined by their physician (excluding other gliptins or GLP-1 agonists). Follow up was for a median of 2.1 years.
No difference was found in the primary end-point of CV death, MI or ischaemic stroke although an increased risk of hospitalisations due to heart failure was found (3.5% vs. 2.8% HR 1.27). Acute pancreatitis was reported in 17 patients (0.2%) receiving saxagliptin and 9 receiving placebo. Chronic pancreatitis occurred in 2 patients taking saxagliptin and 6 in the placebo arm. There were 5 cases of pancreatic cancer in the saxagliptin group and 12 in the placebo group.

PACEF Comment

Following the withdrawal of rosiglitazone, the American Food and Drug Administration (FDA) introduced a requirement for all manufacturers of new treatments for diabetes to conduct post-marketing cardiovascular (CV) outcome studies to fully investigate the CV safety of their drug and to determine whether it had beneficial effects on the macrovascular complications of diabetes.

In this study, saxagliptin did not affect the rate of ischaemic events despite modest improvements in glycaemic control; it did, however, as a secondary outcome, increase the rate of hospitalisation for heart failure. In another study published recently, alogliptin (another DDP-4 inhibitor or 'gliptin' not licensed in the UK) was compared with placebo in 5,380 type 2 diabetics with acute coronary syndrome; similarly, it did not reduce the risk of MI, stroke or death over an average 18 month treatment period. These findings are at odds with an earlier pooled analysis which suggested that gliptins may possibly lower cardiovascular risk.

There is currently some debate about the extent to which DPP-4 inhibitors and GLP-1 agonists increase the risk of pancreatitis and their potential to cause pancreatic cancer. The European Medicines Agency reported on this subject in July 2013 and concluded that no change is currently required to the existing warnings associated with these products; further data will become available from on-going and planned studies which will help to clarify this issue.

References
Scirica BM et al Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013. DOI: 10.1056/NEjMoa307684
European Medicines Agency, *Investigation into GLP-1 based diabetes therapies concluded* (26th July 2013)

NICE TECHNOLOGY APPRAISAL 289: *RUXOLITINIB FOR DISEASE-RELATED SPLENOMEGALY OR SYMPTOMS IN ADULTS WITH MYELOFIBROSIS* (JUNE 2013)

Ruxolitinib is not recommended within its marketing authorisation, that is, for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

PACEF Recommendation:

Ruxolitinib (*Jakavi*) 15mg and 20mg tablets are designated RED-RED for this indication. They are not approved for inclusion in the *Joint Formulary*.

NICE TECHNOLOGY APPRAISAL 291: *PEGLOTICASE FOR TREATING SEVERE DEBILITATING CHRONIC TOPHACEOUS GOUT* (JUNE 2013)

Pegloticase is not recommended within its marketing authorisation, that is, for treating severe debilitating chronic tophaceous gout in adults who may also have erosive joint involvement and in whom xanthine oxidase inhibitors at the maximum medically appropriate dose have failed to normalise serum uric acid, or for whom these medicines are contraindicated.

PACEF Recommendation:
Pegloticase infusion 8mg (*Krystexxa*) is designated RED-RED for this indication. It is not approved for inclusion in the *Joint Formulary*.

NICE TECHNOLOGY APPRAISAL 294: *AFLIBERCEPT SOLUTION FOR INJECTION FOR TREATING WET AGE-RELATED MACULAR DEGENERATION* (JULY 2013)

Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:

- it is used in accordance with the recommendations for ranibizumab in NICE technology appraisal guidance 155 (re-issued in May 2012) **and**
- the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.

Notes

- Aflibercept solution for injection (*Eylea*) is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein which binds to all forms of VEGF-A, VEGF-B and the placental growth factor. The drug works by preventing these factors from stimulating the growth of fragile and permeable new blood vessels associated with wet AMD. It has marketing authorisation for adults for the treatment of neovascular (wet) AMD.
- The recommended dose is 2mg given monthly for 3 consecutive doses followed by one injection every two months. After the first 12 months, the treatment interval may be extended based on visual and anatomic outcomes.
- In comparison, ranibizumab (*Lucentis*) injection is given monthly; the cost difference between monthly ranibizumab and bimonthly aflibercept has been presented to PACEF as potentially cost-saving by ULH Drug and Therapeutic Committee and ULH opthalmologists.

NICE guidance on *Ranibizumab for the treatment of age-related macular degeneration* (May 2012)

NICE TA 294 recommends that aflibercept (*Eylea*) should be used in accordance with the recommendations for ranibizumab already published as follows:

Ranibizumab is recommended for the treatment of wet AMD if all of the following apply:

- the best corrected visual acuity is between 6/12 and 6/96.
- there is no permanent structural damage to central fovea.
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension.
- there is evidence of recent disease progression.

PACEF Recommendation:
Aflibercept solution for injection (*Eylea*) is designated RED for adults for the treatment of neovascular (wet) AMD within NICE criteria. ULH opthalmologists have

suggested that aflibercept may be a lower cost option than ranibizumab in some patients. Aflibercept solution for injection (*Eylea*) is approved for inclusion in the *Joint Formulary* for this indication.

GUIDANCE ON THE USE OF THE SALBUTAMOL METERED DOSE INHALER WITH A SPACER DEVICE

Practitioners are reporting that an increasing number of patients are being advised to use multiple actuations of the salbutamol metered dose inhaler into their spacer device, particularly at times of exacerbation, in an attempt to increase the amount of drug available for inhalation. Prescribers are reminded that there is no evidence that multiple actuations of a salbutamol MDI into a spacer increases the amount of drug available for inhalation. British Thoracic Guidelines clearly state that in order to maximise drug delivery, single actuations should be used prior to inhalation. Multiple actuations of salbutamol into a spacer device actually decrease the amount of respirable drug available because agglomeration of the particles increases their size and displaces the aerosol out of the spacer or onto the spacer walls; electrostatic attraction of the particles to the wall of the spacer and to each other also occurs. Multiple actuations within a spacer device have been shown to reduce the amount of respirable drug available by almost two thirds. This is particularly important when the dose delivered needs to be high, as in the treatment of an exacerbation.

BTS guidelines advocate that the drug should be administered by repeated single actuations of the MDI into the spacer, each followed by inhalation. Administering each dose separately increases the amount of drug available for inhalation by over 20%.

BTS guidelines read as follows:

- The spacer device should be compatible with the pMDI being used.
- The drug should be administered by repeated single actuations of the metered dose inhaler into the spacer, each followed by inhalation.
- There should be minimal delay between pMDI actuation and inhalation.
- Tidal breathing is as effective as single breaths.
- Spacers should be cleaned monthly rather than weekly as per the manufacturer's recommendations or performance is adversely affected. They should be washed in detergent and allowed to dry in air to reduce any static that drying with a cloth would produce. The mouthpiece should be wiped clean of detergent before use.
- Drug delivery may vary significantly due to static charge. Metal and other antistatic spacers are not affected in this way.
- Plastic spacers should be replaced at least every 12 months, but some may need changing at six months.

It is also important that patients have their ability to use a spacer device assessed by a competent healthcare professional and that inhaler technique should be reassessed regularly as part of a structured clinical review. Assessment should take place on hospital admissions with significant issues highlighted on the discharge summary.

PACEF Recommendation:
Where a salbutamol MDI is used in conjunction with a spacer device the required dose should be administered by repeated single aspirations into the spacer followed by inhalation, rather than by multiple actuations into the spacer. Evidence suggests that administering each dose separately increases the amount of drug available for inhalation by over 20%.

References:
British Thoracic Society Guidelines via www.brit-thoracic.org.uk

Barry. P.W and O Callaghan C (1994) Multiple actuations of salbutamol MDI into a spacer device reduce the amount of drug recovered in the respirable range. *European Respiratory Journal* 7 pp 1707 – 1709.

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