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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 9; Number 1 **February 2015**

What's new this month?

- **The Lincolnshire PACEF website has moved to: http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef . Alternatively, go to http://lincolnshire-pacef.nhs.uk and follow the commissioning link to the PACEF section (see page 3).**
- **Naltrexone 50mg tablets are approved for use for the unlicensed indication of pruritis linked to cholestasis, renal failure or liver disease. The product is designated AMBER without shared care for this indication and should only be prescribed in primary care following initiation by a gastroenterologist or dermatologist (see page 3).**
- **Pipotiazine palmitate injection (*Piportil Depot*) 50mg/ml for maintenance therapy in schizophrenia and other psychoses is to be withdrawn from the end of March 2015. It is designated RED-RED and should not be initiated in new patients. Existing patients will need to be reviewed and switched to an alternative treatment. Where possible, GPs are advised to contact the LPFT consultant associated with the patient for further advice prior to switching to an alternative. Where the patient is no longer under the care of the LPFT hosted service, a referral should be made (see page 4).**
- **There is currently a supply problem with haloperidol 500 microgram capsules. If a dose below 1.5mg is required, the only option is to prescribe a haloperidol liquid formulation. Where a 1mg in 5ml *Tariff* special is indicated, the lower cost 1mg in 5ml oral solution should be prescribed rather than the oral suspension (see page 4).**
- **The *CoaguChek XS PT* system and *INRatio2 PT/INR* monitor are recommended for self-monitoring coagulation status in adults and children on long term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease. Patients must be trained in the use of the coagulometer and their equipment must be regularly calibrated to ensure precision and accuracy. The patient's competence to check their own coagulation status must also be regularly confirmed. This form of testing is only approved for patients with atrial fibrillation; it is not approved for deep vein thrombosis or pulmonary embolism. Standard INR monitoring should always be considered in preference. Where self-monitoring is indicated, *CoaguChek XS PT* is recommended in preference to *InRatio2 PT/INR*. *CoaguChek XS PT* test strips and *InRatio2 PT/INR* are both designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*. Neither of the associated coagulometers is available on NHS prescription. Where an appropriate patient wishes to self-test and is judged competent to do so, the relevant coagulometer must be purchased by the patient (see page 5).**
- **Despite a RED classification confining the product to psychiatrist use only and specific guidance from NICE recommending that the product should not be used for the treatment of major depressive episodes, agomelatine tablets 25mg (*Valdoxan*) continue to be prescribed in Lincolnshire primary care. In all remaining patients receiving agomelatine in primary care, MHRA safety advice around liver function monitoring must be followed (see page 6).**

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SUMMARY OF PACEF DECISIONS: *DECEMBER 2014 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Agomelatine 25mg tablets (*Valdoxan*) (Servier)	For major depression.	RED Included in the *Lincolnshire Joint Formulary* for this indication.
Boceprevir capsules 200mg (*Victrelis*) (MSD)	Licensed in combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 in patients with compensated liver disease	RED Included in the *Lincolnshire Joint Formulary* for this indication. All baseline checks and routine monitoring will remain the responsibility of hospital based services.
CoaguChek XS PT diagnostic test (Roche Diagnostics)	Quantitative determination of prothrombin time in capillary or venous whole blood in range 0.8 to 8.0 INR. For use with *CoaguChek XS* meter	GREEN Recommended in preference to *INRatio* diagnostic test. Included in the *Lincolnshire Joint Formulary* for this indication. Standard INR monitoring should always be considered in preference.
Colistimethate sodium dry powder for inhalation (*Colobreathe*) 1.66 million units per Capsule (Forest)	For the treatment of chronic pulmonary infection caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis over 6 years.	AMBER with shared care. Included in the *Lincolnshire Joint Formulary* for this indication.
Dabrafenib 50mg and 75mg capsules (*Tafinlar*)	For use as monotherapy for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
INRatio diagnostic test (Alere)	Quantitative determination of prothrombin time in capillary whole blood in range 0.7 to 7.5 INR. For use with *Alere INRatio* meter	GREEN *CoaguChek XS PT* diagnostic test Is recommended in preference to *INRatio* diagnostic test. Included in the *Lincolnshire Joint Formulary* for this indication. Standard INR monitoring should always be considered in preference.
Lenalidomide 5mg, 10mg, 15mg and 25mg capsules (*Revlimid*)	For the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.

	5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.	
Naltrexone 50mg tablets	For pruritis due to cholestasis, renal failure or liver disease (unlicensed gastroenterology and dermatology indication).	AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Pipotiazine palmitate (*Piportil Depot*) 50mg/ml injection 1ml and 2ml ampoules (Sanofi)	For maintenance therapy in schizophrenia and other psychoses.	RED-RED To be removed from the *Lincolnshire Joint Formulary* for this indication.
Ponatinib 15mg tablets (*Iclusig*)	For adults with chronic myeloid leukaemia or Philadelphia-chromosome-positive acute lymphoblastic leukaemia.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Telaprevir tablets 375mg (*Incivo*) (Janssen-Cilag)	Licensed in combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 in patients with compensated liver disease	RED Included in the *Lincolnshire Joint Formulary* for this indication. All baseline checks and routine monitoring will remain the responsibility of hospital based services.

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 PACEF website (http://lincolnshire-pacef.nhs.uk); follow the commissioning link to PACEF. Electronic copies 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.

Google searching can be a quick and effective way of finding back numbers of the *PACE Bulletin* relevant to a specific topic of interest. Searchers are advised to use the official version of the *Bulletin* available from the PACEF website rather than depend on a potentially unreliable draft or variant found through Google or an alternative search engine.
The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

IMPORTANT CHANGES TO THE PACEF WEBSITE

Effective immediately, the Lincolnshire PACEF website has moved to:

http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef

Alternatively go to http://lincolnshire-pacef.nhs.uk and follow the commissioning link to the PACEF section. This will be the new home for all PACEF publications in 2015. We are planning a complete refresh of the website early in the New Year. We apologise for any inconvenience caused by the temporary loss of the website earlier in December; we have now resolved these problems and normal service has been resumed.

NEW DRUG ASSESSMENT: *NALTREXONE 50MG TABLETS FOR PRURITIS DUE TO CHOLESTASIS (UNLICENSED DERMATOLOGY INDICATION)*

PACEF have ratified a decision made by United Lincolnshire Hospitals Drug and Therapeutics Committee to approve unlicensed naltrexone 50mg tablets for pruritis due to cholestasis, renal failure or liver disease. ULH dermatologists envisage that there will be no more than 2 to 3 patients per year.

PACEF Recommendation:
Naltrexone 50mg tablets are approved for use for the unlicensed indication of pruritis linked to cholestasis, renal failure or liver disease. The product is designated AMBER

without shared care for this indication and should only be prescribed in primary care following initiation by a gastroenterologist or dermatologist It is approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.

DISCONTINUATION OF PIPOTHIAZINE PALMITATE 50MG/ML INJECTION (*PIPORTIL DEPOT*)

Sanofi wrote out to all healthcare professionals in October 2014 providing advance warning of their intention to discontinue pipotiazine palmitate (*Piportil Depot*) 50mg/ml injection 1ml and 2ml amps from the end of March 2015. This is due to a global shortage of the active ingredient pipotiazine palmitate. Prescribers are advised that:

- No new patients should be initiated on pipotiazine palmitate.
- Existing patients should be reviewed with a view to switching to an alternative treatment.

Review of prescribing data suggests that there is very little use of the product across the county.

PACEF Recommendation:
Pipotiazine palmitate injection (*Piportil Depot*) 50mg/ml for maintenance therapy in schizophrenia and other psychoses is to be withdrawn from the end of March 2015. It is designated RED-RED and should not be initiated in new patients. Existing patients will need to be reviewed and switched to an alternative treatment. Where possible, GPs are advised to contact the LPFT consultant associated with the patient for further advice prior to switching to an alternative. Where the patient is no longer under the care of the LPFT hosted service, a referral should be made.

SUPPLY PROBLEMS WITH HALOPERIDOL 500 MICROGRAM CAPSULES

There is currently a supply problem with haloperidol 500 microgram capsules. If a dose below 1.5mg is required the only option is to prescribe a haloperidol liquid formulation. There will be cost implications associated with this as follows:

Haloperidol 500microgram capsules (generic)	£1.18 for 30 (4p per dose)
Haloperidol 5mg in 5ml oral solution	£6.41 for 100ml (3.2p per 0.5ml dose)
Haloperidol 1mg in 5ml oral solution (*Tariff* Special)	£81.26 for 200ml (£1.01 per 2.5ml dose)
Haloperidol 1mg in 5ml oral suspension (*Tariff* Special)	£111.89 for 100ml (£2.79 per 2.5ml dose)

Reference: *Drug Tariff* January 2015

Where a 1mg in 5ml Tariff special is indicated, the lower cost 1mg in 5ml oral solution should be prescribed rather than the oral suspension.

NICE TECHNOLOGY APPRAISAL 321 *DABRAFENIB FOR TREATING UNRESECTABLE OR METASTATIC BRAF V600 MUTATION-POSITIVE MELANOMA* (OCTOBER 2014)

Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme.

Dabrafenib is a BRAF kinase inhibitor licensed as monotherapy for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.

PACEF Recommendation:
Dabrafenib 50mg and 75mg capsules (*Tafinlar*) are designated RED and approved for specialist use only for this indication. They are already approved for use through the *Lincolnshire Joint Formulary* in accordance with *National Cancer Drugs Fund List* criteria.

NICE TECHNOLOGY APPRAISAL 322: *LENALIDOMIDE FOR TREATING MYELODYSPLASTIC SYNDROMES ASSOCIATED WITH AN ISOLATED DELETION 5Q CYTOGENETIC ABNORMALITY* (SEPTEMBER 2014)

Lenalidomide is recommended as an option, within its marketing authorisation (i.e. for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality), when other therapeutic options are insufficient or inadequate, with the following condition:

- The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the company.

Lenalidomide (*Revlimid*) is licensed for the treatment of multiple myeloma in adult patients who have received at least one prior therapy in combination with dexamethasone. It is also licensed for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

PACEF Recommendation:
Lenalidomide 5mg, 10mg, 15mg and 25mg capsules (*Revlimid*) are designated RED for this indication and approved for inclusion in the *Lincolnshire Joint Formulary*. They already appear in the Formulary for use in multiple myeloma (in accordance with NICE TA171). Lenalidomide is also included in the National Cancer Drugs Fund List for two indications where specific criteria are met: (1) the second line treatment of multiple myeloma and (2) the treatment of myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality.

NICE DIAGNOSTIC GUIDANCE 14: *ATRIAL FIBRILLATION AND HEART VALVE DISEASE: SELF-MONITORING COAGULATION STATUS USING POINT-OF-CARE COAGULOMETERS (COAGUCHEK XS AND INRATIO2 PT/INR MONITOR)(SEPTEMBER 2014)*

The *CoaguChek XS* system is recommended for self-monitoring coagulation status in adults and children on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if:

- the person prefers this form of testing **and**
- the person or their carer is both physically and cognitively able to self-monitor effectively.

The *InRatio2 PT/INR* monitor is recommended for self-monitoring coagulation status in adults and children on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if:

- the person prefers this form of testing **and**
- the person or their carer is both physically and cognitively able to self-monitor effectively.

Although there is greater uncertainty of clinical benefit for the *InRatio2 PT/INR* monitor than for the *CoaguChek XS* system, the evidence indicates that the precision and accuracy of both monitors are comparable to laboratory-based INR testing.

Patients and carers should be trained in the effective use of the *CoaguChek XS* system or the *INRatio2 PT/INR* monitor and clinicians involved in their care should regularly review their ability to self-monitor.

Equipment for self-monitoring should be regularly checked using reliable quality control procedures, and by testing patients' equipment against a healthcare professional's coagulometer which is checked in line with an external quality assurance scheme. Ensure accurate patient records are kept and shared appropriately.

For people who may have difficulty with or who are unable to self-monitor, such as children or people with disabilities, their carers should be considered to help with self-monitoring

PACEF Recommendation

The *CoaguChek XS PT* system and *INRatio2 PT/INR* monitor are recommended for self- monitoring coagulation status in adults and children on long term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease. Patients must be trained in the use of the coagulometer and their equipment must be regularly calibrated to ensure precision and accuracy. The patient's competence to check their own coagulation status must also be regularly confirmed. This form of testing is only approved for patients with atrial fibrillation; it is not approved for deep vein thrombosis or pulmonary embolism. Standard INR monitoring should always be considered in preference. Where self-monitoring is indicated, *CoaguChek XS PT* is recommended in preference to *InRatio2 PT/INR*. *CoaguChek XS PT* test strips and *InRatio2 PT/INR* are both designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary.* Neither of the associated coagulometers/INR monitors is available on NHS prescription. Where an appropriate patient wishes to self-test and is judged competent to do so, the relevant coagulometer must be purchased by the patient.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (NOVEMBER 2014)

AGOMELATINE (*VALDOXAN*): RISK OF LIVER TOXICITY- REMINDER TO TEST LIVER FUNCTION BEFORE AND DURING TREATMENT

The MHRA first notified prescribers about the risk of hepatotoxicity associated with agomelatine in October 2012 following the publication of several case reports. A recent European wide review revealed poor compliance with safety recommendations around of monitoring liver function. In response to these findings, the MHRA has re-issued its advice to healthcare professionals:

- Perform baseline liver function tests in every patient before starting treatment with agomelatine.
- Do not start treatment if serum transaminases exceed three times the upper limit of normal.
- Monitor liver function at 3, 6, 12, and 24 weeks after starting treatment and regularly thereafter when clinically indicated.
- Stop treatment immediately if serum transaminases exceed three times the upper limit of normal, or if the patient has symptoms or signs of suspected liver injury.
- Advise patients to watch out for the symptoms and signs of liver injury (e.g. jaundice, dark urine, bruising) and explain the importance of regular liver function monitoring.

- Advise patients to stop taking agomelatine and to get medical help immediately if they have any signs or symptoms of liver injury.

PACEF Comment
Despite a RED classification confining the product to psychiatrist use only and specific guidance from NICE recommending that the product should not be used for the treatment of major depressive episodes, agomelatine tablets 25mg (*Valdoxan*) continue to be prescribed in Lincolnshire primary care. In all remaining patients receiving agomelatine in primary care, MHRA safety advice around liver function monitoring must be followed.

COLOBREATHE (COLISTIMETHATE SODIUM DRY POWDER FOR INHALATION): RISK OF CAPSULE BREAKAGE - NEW INSTRUCTIONS FOR USE

The MHRA have received reports of *Colobreathe* (colistimethate sodium) capsules shattering when pierced by the inhaler device. The instructions for inhaler use have been revised to reduce this risk. The MHRA advises that health care professionals should demonstrate the new inhaler instructions to patients and carers and supervise the first dose. The key points are:

- insert the capsule widest end first into the inhaler chamber.
- pierce the capsule gradually using a two-step process.
- only pierce each capsule once.

PACEF Comment:
Colistimethate sodium dry powder for inhalation (*Colobreathe*) 1.66 million units per capsule is licensed for the treatment of chronic pulmonary infection caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis over 6 years. Analysis of primary care prescribing data suggests that there is no GP prescribing of this product in Lincolnshire at present. Nonetheless, colistimethate sodium dry powder for inhalation (*Colobreathe*) is designated AMBER with shared care for this indication and is approved for use through the *Lincolnshire Joint Formulary.*

BOCEPREVIR (*VICTRELIS*) AND TELAPREVIR (*INCIVO*): BASELINE PREDICTIVE FACTORS FOR SEPSIS, WORSENING LIVER FUNCTION, AND MORTALITY

Boceprevir (*Victrelis*) and telaprevir (*Incivo*) are protease inhibitors indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease. A European review identified the following baseline markers as predictive factors for morbidity requiring hospitalisation (e.g. sepsis, worsening liver function) and mortality in cirrhotic patients treated with either boceprevir or telaprevir in combination with peginterferon alfa and ribavirin:

- low platelet count
- hypoalbuminaemia
- coagulopathy (for boceprevir only)

Boceprevir and telaprevir are not recommended for patients who have a low platelet count or hypoalbuminaemia before starting. Initiation of boceprevir is also not recommended for patients who have coagulopathy. If treatment is started, closely monitor for infection, worsening liver function, and anaemia.

PACEF Comment
Both boceprevir capsules 200mg (*Victrelis*) and telaprevir tablets 375mg (*Incivo*) are approved for use within licensed indications as RED hospital-only medicines. All

baseline checks and routine monitoring will remain the responsibility of hospital based services. Both products are included in the *Lincolnshire Joint Formulary*.

PONATINIB (*ICLUSIG*): RISK OF VASCULAR OCCLUSIVE EVENTS

Ponatinib (*Iclusig*) is licensed for adults with chronic myeloid leukaemia or Philadelphia-chromosome-positive acute lymphoblastic leukaemia. It has a marketing authorisation that restricts it's use to patients who have limited alternative treatment options. The MHRA alerted prescribers to the risk of serious vascular occlusive events with ponatinib in December 2013. Subsequently, an in-depth European wide review has concluded that the risk of blood vessel blockage with ponatinib is likely to be dose-dependent. However, at this stage, the data is insufficient to justify a reduction of the ponatinib dose. Also, there is a risk that a lower dose might not be as effective in all patients and in long-term treatment. Therefore, the recommended starting dose of ponatinib remains at 45 mg once a day.

The product information will be updated with strengthened warnings about the risks associated with ponatinib. The latest evidence will also be added with the advice to consider reducing the dose in patients with chronic phase chronic myeloid leukaemia who are responding well to treatment, but who are at high risk of blood vessel blockage. Prescribers are advised to stop ponatinib if a complete response has not occurred within 3 months of treatment and to monitor patients for high blood pressure or signs of heart problems.

PACEF Comment
Ponatinib 15mg tablets (*Iclusig*) are approved for use within license and are designated RED for hospital-use only in accordance with the *National Cancer Drugs Fund List.* Ponatinib is included within the *Lincolnshire Joint Formulary*. It is expected that all baseline checks and routine monitoring of patients prescribed this therapy would remain the responsibility of a hospital based service.

CHLORHEXIDINE SOLUTIONS: REMINDER OF THE RISK OF CHEMICAL BURNS IN PREMATURE INFANTS

Advice for healthcare professionals:

- When using alcohol-based or water-based chlorhexidine solutions on premature infants, bear in mind the risk of severe chemical injuries.
- Use the minimum amount of chlorhexidine solution required and do not allow the solution to pool. Remove any excess solution and any soaked materials, drapes, or gowns from the skin.
- Monitor patients frequently to detect and manage cutaneous side effects at an early stage.
- Please report any adverse events through the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

DESICCANTS IN BLISTER PACKS: REMINDER OF RISK OF INGESTION

During the past two months, the MHRA have received two reports of people swallowing the desiccant that came with their nicorandil tablets rather than the tablet itself. Neither of the people suffered any adverse effects. The foil of blister packs containing desiccant is clearly labelled to show which blister pocket contains the desiccant. The accompanying patient information leaflet also advises people not to swallow the desiccant.

PACEF Comment
Patients receiving supplies of nicorandil should be informed that the blister pack contains a desiccant that should not be swallowed. Community pharmacies and dispensing practices are asked to bring this to the attention of patients when nicorandil is dispensed.

NHS ENGLAND, PATIENT SAFETY ALERT: *RISK OF DISTRESS AND DEATH FROM INAPPROPRIATE DOSES OF NALOXONE IN PATIENTS ON LONG-TERM OPIOID/OPIATE TREATMENT* (NOVEMBER 2014)

Naloxone is an opioid/opiate antagonist licensed for use in:

- complete or partial reversal of central nervous system depression and especially respiratory depression, caused by natural or synthetic opioids and
- treatment for suspected acute opioid overdose or intoxication.

Naloxone must be given with great caution to patients who have received longer-term opioid/opiate treatment for pain or who are physically dependent on opioids/opiates. The use of naloxone in patients where it is not indicated or in larger than recommended doses can cause rapid reversal of the physiological effects of pain control resulting in intense pain and distress. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest may result from inappropriate doses of naloxone being used in these patients.

NHS England have received details of three patient safety incidents describing failure to follow *BNF* guidance in relation to the appropriate use and recommended dosage of naloxone in these patients. Two of these incidents resulted in death.

Acknowledgements
Many thanks to: Cathy Johnson, Interface Lead Pharmacist, Robyn Thompson, Senior Pharmacist, United Lincolnshire Hospitals Trust and Shiraz Haider, Chief Pharmacist, Lincolnshire Partnership Foundation Trust for their help with the compilation of this *Bulletin*.

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February 2015