Lincolnshire Prescribing and Clinical Effectiveness (PACE) Bulletin

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Drug Assessments

Product	Summary	Decision
Rivaroxaban 2.5mg tablets (Xarelto ®)	**Introduction:** The marketing authorisation for rivaroxaban (Xarelto®) has been extended to include use with acetylsalicylic acid (aspirin), for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. ULHT cardiology team have requested that rivaroxaban is added to the formulary for the treatment of this condition. Dose - rivaroxaban 2.5mg twice daily with aspirin 75mg once daily for long term use **Further relevant information:** Rivaroxaban is already included on the Lincolnshire formulary with a range of traffic light classifications (Red, Amber, Green) depending on its licensed use. Use will be in line with the licensed indication in patients with high risk for ischaemic events who have multi-vessel coronary artery disease and concomitant vascular disease. The number of patients, where this treatment is indicated is estimated to be low, around 50 patients across the local area. Clinical evidence shows the addition of rivaroxaban to standard aspirin therapy significantly reduces the risk of a composite of cardiovascular death, stroke or myocardial infarction. However there is a significant increase in major bleeding events, but the incidence of intracranial or fatal bleed is not significantly greater. Treatment on this combination will be initiated by secondary care and patients will be provided with information provided by the manufacturer, on increased bleeding risk.	Rivaroxaban 2.5mg tablets approved for inclusion onto the formulary classed as AMBER 2 for this licensed indication.
Hydrocortisone 0.335% single use preservative free eye drops (Softacort®)	**Introduction:** These drops are indicated for short term use (typically 2 weeks) in the treatment of mild non-infectious allergic or inflammatory conjunctival diseases, including Dry Eye Disease (DED). Treatment should only be initiated by ophthalmic specialists. **Further relevant information:** Hydrocortisone is a less potent corticosteroid than those in the currently used ophthalmic preparations i.e. dexamethasone and prednisolone, and it is more suitable for mild inflammation. Furthermore, it may be associated with a lower incidence of raised intraocular pressure (IOP). Softacort® also offers cost savings when used in place of other available preservative-free corticosteroid eye drops for mild disease.	Approved for inclusion onto the formulary as AMBER 2

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	ULHT consultants expect low use i.e. up to 3 patients per month across the county. They state the ability to prescribe hydrocortisone, the lowest potency corticosteroid molecule, is attractive because higher potency is correlated with an increased risk of intraocular pressure rises. Softacort® is contraindicated and used with caution in the same conditions as more potent topical corticosteroids.	
Insulin Lispro Sanofi 100units/ml.	**Introduction:** This is a new biosimilar insulin lispro which has identical licensed indications as the originator product Insulin Lispro (Humalog). Insulin Lispro Sanofi is available in the same presentations as the Humalog brand: • a vial • a prefilled pen (Solostar device) • a cartridge for use in a pen device. The cartridges should be used in Junior STAR pen (which delivers insulin lispro Sanofi in 0.5 unit dose increments) and the Tactipen, AllStar and AllStar PRO pens (which deliver Insulin Lispro Sanofi in 1 unit dose increments). **Further relevant information:** Insulin Lispro Sanofi needs to be prescribed by brand (as is standard advice for all insulin products). The PACEF approved product is to be used for new patients when insulin lispro is indicated and for those patients with suboptimal control on their existing insulin who are having a review of their treatment. The Humalog brand of insulin lispro is also available in a 200units/ml strength and should be continued to be initiated when patients require the higher strength. Humalog also available as biphasic insulin in combination with protamine: • Humalog Mix25 - Insulin lispro/insulin lispro protamine 25%/75% susp, 100 units/ml. • Humalog Mix50 -Insulin lispro/insulin lispro protamine 50%/50% susp, 100 units/ml. These products remain on the formulary as a treatment option when the use of a biphasic insulin is indicated.	Approved for inclusion onto the formulary as GREEN. Approved for use in new patients, when insulin lispro 100units/ml is clinically indicated and for those with suboptimal control on their existing insulin who are having a review of their treatment.
Mexiletine 167mg capsules (Namuscula®)	**Introduction:** This licensed formulation of mexiletine (Namuscula®) has recently been launched in UK. It is licensed for the symptomatic treatment of myotonia in adult patients with non- dystrophic myotonic disorders. An unlicensed formulation of mexiletine 200mg is currently included onto the formulary for the treatment of life-threatening ventricular arrhythmias. It is also included on the formulary for the treatment of neurological indications. In both instances it is classed as AMBER 2. **Further relevant information:** Since this licensed product has been made available ULHT have been informed that importer companies are no longer able to supply the unlicensed formulation, unless there is specific clinical need, due to there now being a licensed UK	Namuscula® 167mg brand of mexiletine is approved for inclusion onto the formulary, as Amber 2.

Product	Summary	Decision
	product. Namuscula® is not licensed for use for either cardiology or neurology indications, so use for these conditions will be classed as "off-label - unlicensed use". **The licensed product is marketed as strength of 167mg mexiletine base (which is equivalent to 200mg of mexiletine hydrochloride).** **PACEF is aware of potential for confusion. Use of mexiletine is very limited. Where we are aware that mexiletine is being prescribed in primary care, clinicians will be contacted and made aware of the availability of Namuscula®.**	
Akizza® 20/75mg - Ethinylestradiol 20 microgram/ gestodene 75 microgram tablets **Akizza® 30/75mg - Ethinylestradiol 30 microgram /gestodene 75 microgram tablets**	**Introduction:** New combined oral contraceptive pill containing combination of ethinylestradiol and gestodene. **Further relevant information:** Cost comparison of existing ethinylestradiol/gestodene combinations shows Akizza is not most cost effective option. Akizza formulations are therefore not approved for inclusion onto the formulary. For reference, formulary approved combinations and products are: <u>Ethinylestradiol 20 microgram/gestodene 75 microgram</u> Aidulan® 20/75 Millinette® 20/75 Sunya® 20/75 <u>Ethinylestradiol 30 microgram/gestodene 75 microgram</u> Aidulan® 30/75 Millinette® 30/75 Katya® 30/75	Akizza® 20/75mg - Ethinylestradiol 20 microgram/ gestodene 75 microgram tablets Akizza® 30/75mg - Ethinylestradiol 30 microgram/gestodene 75 microgram tablets. Not approved for use, classed as RED/RED.
Sodium Valproate sustained release – Epival CR® tablets,300mg & 500mg,	**Introduction:** New sodium valproate MR product available, licensed for the treatment of epilepsy, psychosis and mania. **Further relevant information:** A number of different sustained release formulations of sodium valproate are already included on the formulary covering different licensed indications**.** PACEF members were concerned at the potential for confusion if another brand is added to formulary. Epival CR was not approved for inclusion not the formulary. **Reminder: All sustained release sodium valproate products should be prescribed by brand name.**	Epival CR not approved for inclusion not the formulary. Classed as RED/RED.
Solifenacin oral suspension 1mg/ml (Vesicare®)	**Introduction:** Solifenacin oral suspension (Vesicare®) is licensed for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder (OAB) syndrome. It is also licensed for treatment of neurogenic detrusor overactivity (NDO) in	Approved for inclusion onto the formulary as GREEN.

Product	Summary	Decision
	paediatric patients aged 2 to 18 years. **Further relevant information:** Before the licensed oral solution was launched the only option for patients unable to take solifenacin tablets was to use an unlicensed oral suspension which is prohibitively expensive. The licensed formulation is at a dose of 5mg/5ml is the same cost as a Vesicare® 5mg tablet. The licensed solution is approved for use for patients when solifenacin therapy is indicated and a tablet dosage form is considered not appropriate e.g. when the patient has confirmed swallowing difficulties, or for use within the licensed indication for children.	

Enoxaparin (Inhixa) pre-filled syringes - deployment of the needle guard, difference to that of clexane brand.

As a result of the continued supply shortages associated with the Clexane® brand of enoxaparin United Lincolnshire Hospitals (ULH) have added the Inhixa® brand of enoxaparin to the formulary, as an alternative when Clexane® is not available. Inhixa® is a biosimilar of enoxaparin which is licensed for the same indications and at the same dose as the originator product.The majority of treatment with enoxaparin is initiated within secondary care or on the advice of a specialist.

There is a difference in syringe design with regard to deployment of the needle guard after use:

- With Clexane® the guard is automatically deployed, however for Inhixa®, after withdrawing the needle from the injection site, the plunger needs to be pushed hard to activate the needle guard.
- The manufactures of Inhixa® have produced a short video depicting the difference between the two syringes which can be accessed following this link: https://www.youtube.com/watch?v=E8AytPojtVI

MEDICINES AND HEALTHCARE REGULATORY AGENCY (MHRA): DRUG SAFETY UPDATE (January 2019)

Tapentadol: Risk of seizures and reports of serotonin syndrome when co-administered with other medicines

Tapentadol is classed as RED/RED on Lincolnshire formulary. However it is classed as AMBER 2 for use when treatment is initiated by Nottinghamshire pain team in accordance with their guidance.

MHRA have issued the following advice for healthcare professionals:

- As for all opioid medicines tapentadol can cause seizures.
- Tapentadol should be prescribed with care in patients with a history of seizure disorders or epilepsy.
- Tapentadol may increase seizure risk in patients taking other medicines that lower seizure threshold, e.g. antidepressants such as serotonin reuptake inhibitors (SSRI's), serotonin – noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants and antipsychotics.
- Serotonin syndrome has been reported when tapentadol is used in combination with serotoninergic antidepressants.
- Withdrawal of the serotonergic medicine, together with supportive symptomatic care, usually brings about a rapid improvement in serotonin syndrome.

- Report suspected adverse drug reactions, including those resulting from interactions between drugs on a yellow card.

Ipilimumab: Reports of cytomegalovirus (CMV) gastrointestinal infection or reactivation.

Ipilimumab is classed as RED for hospital use only on Lincolnshire formulary.

MHRA have issued the following advice for healthcare professionals:

- Colitis commonly occurs in patients treated with ipilimumab for advanced melanoma. Patients should be advised to contact their healthcare professional immediately at the onset of symptoms of colitis (including diarrhoea, blood in stools or abdominal pain)
- If patients on ipilimumab present with diarrhoea or colitis, investigate possible causes, including infections, perform a stool infection work-up and screen for CMV.
- For patients with immune-related colitis that is corticosteroid refractory, use of an additional immunosuppressive agent should only be considered if other causes are excluded, including CMV infection or reactivation.

Please refer to the MHRA drug safety update Vol 12 issue 6 and the summary of product characteristics for further detail.

MEDICINES AND HEALTHCARE REGULATORY AGENCY (MHRA): DRUG SAFETY UPDATE (February 2019)

Carbimazole: Increased risk of congenital malformations, and risk of acute pancreatitis.

Carbimazole is classed as GREEN on Lincolnshire formulary.

MHRA have issued the following advice for healthcare professionals:
Increased risk of congenital malformations

- Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, particularly in the first trimester of pregnancy and at high doses (15mg or more daily)
- Women of child bearing potential should use effective contraception during treatment with carbimazole.
- Carbimazole should only be considered in pregnancy after a through individual assessment of benefits and risks of treatment and only at the lowest effective dose without administration of thyroid hormones close maternal, foetal and neonatal monitoring is recommended.
- Report suspected adverse drug reactions, associated with medicines taken during pregnancy experienced by women, or the baby or child.

Risk of acute pancreatitis

- Cases of acute pancreatitis have been reported very infrequently during treatment with carbimazole.
- If acute pancreatitis occurs, stop carbimazole treatment immediately.
- Do not use carbimazole in patients with history of acute pancreatitis in association with previous treatment.
- Re-exposure may result in life threatening acute pancreatitis with a decreased time to onset.
- Report suspected adverse drug reactions, to the yellow card scheme.

SGLT2 inhibitors reports of Fournier's gangrene

The following SGLT-2 inhibitors: dapagliflozin, canagliflozin and empagliflozin are included on the Lincolnshire formulary as both monotherapy and in combination with metformin. All formulations are classed as GREEN.

MHRA have issued the following advice for healthcare professionals:

- Post marketing cases of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) have been associated with the use of SGLT-2 inhibitors.
- Fournier's gangrene is a rare but serious and potentially life threatening infection.
- If Fournier's infection is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required)
- Urogenital infection or perineal abscess may precede necrotising fasciitis.
- Advise patients to seek urgent medical attention if they experience severe pain, tenderness, erythema or swelling in the genital or perineal area, accompanied by fever or malaise.
- Report suspected adverse drug reactions, to the yellow card scheme

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