Arden and 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 10; Number 6 **May 2016**

What's new this month?

- ***AirFluSal Forspiro 50/500*** **is a new salmeterol/fluticasone combination dry powder inhaler licensed for the treatment of COPD in adults. Comparative evidence suggests equivalent efficacy and safety to the *Seretide Accuhaler 500*; *AirFluSal Forspiro* is also lower cost. *AirFluSal Forspiro 50/500* is designated GREEN and preferred for new patients; therapeutic switching is advocated as part of the 2016/17 QIPP Programme (see page 4).**
- ***Fostair 200/6*** **metered dose inhaler and *Fostair 200/6 NEXThaler* are approved for use as cost-effective alternatives to higher cost equivalent products such as *Seretide Evohaler 250/25*, *Seretide Accuhaler 500* and *Symbicort Turbohaler 400/12.* Both products are designated GREEN (see page 6).**
- **Supply problems are beginning to emerge around two specialist cardiovascular medicines: amiodarone 100mg and 200mg tablets and flecainide acetate 50mg and 100mg tablets. As both amiodarone and flecainide are designated AMBER, changes to therapy should not be implemented without specialist advice and support (see page 9).**
- **New resources have been launched to highlight the risk of developmental disorders and congenital malformations in children exposed to sodium valproate in utero (see page 10).**
- **Monitoring of blood electrolytes is essential in patients co-prescribed a potassium-sparing diuretic, like spironolactone, in combination with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) for heart failure. Concomitant use of spironolactone with an ACEI or ARB is not routinely recommended because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment (see page 12).**
- **Vortioxetine 5mg, 10mg and 20mg tablets (*Brintellix*) are approved for third line use in the treatment of adults having a first or recurrent major depressive episode, if the current episode has not responded to two previous antidepressants. Designation: AMBER without shared care. The first two monthly prescriptions will be issued by specialist mental health services with the prospect of ongoing GP prescribing in those that respond (see page 13).**

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SUMMARY OF PACEF DECISIONS: *MARCH 2016 UPDATE*

Device, Dressing or Drug	Indication(s)	Traffic Light and *Joint Formulary* Status
Beclometasone dipropionate 200 microgram/formoterol 6microgram per actuation (*Fostair 200/6 metered dose inhaler*) (Chiesi Ltd)	For the regular treatment of asthma in adults) where the use of a combination ICS/LABA is considered appropriate (i.e. in patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta2-agonist or in patients already adequately controlled on both ICS and LABA).	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary.*
Beclometasone dipropionate 200 microgram/formoterol 6microgram per actuation (*Fostair 200/6 NEXThaler*) (Chiesi Ltd)	For the regular treatment of asthma in adults where the use of a combination ICS/LABA is considered appropriate (i.e. in patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta2-agonist or in patients already adequately controlled on both ICS and LABA).	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary.*
Cinacalcet 30mg, 60mg and 90mg tablets (*Mimpara*) (Amgen)	For secondary hyperparathyroidism in patients with end-stage renal disease on dialysis , as part of a regimen including phosphate binders and /or vitamin D.	AMBER with shared care. Shared care guideline available. Included in the *Lincolnshire Joint Formulary.*
Eltrombopag 25mg and 50mg tablets (Revolade) (Novartis Pharmaceuticals UK Ltd)	For treating severe aplastic anaemia refractory to immunosuppressive therapy	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*.
Enzalutamide 40mg capsules (*Xtandi*) (Astellas Pharma Ltd)	For treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated	RED Approved for inclusion in the *Lincolnshire Joint Formulary*.

Nintedanib 100mg and 150mg capsules (*Ofev*) (Boehringer Ingelheim Limited)	For treating idiopathic pulmonary fibrosis	RED Likely to be prescribed within tertiary centres only. Approved for use within the *Lincolnshire Joint Formulary.*
Nivolumab 10mg/ml concentrate for solution for infusion (*Opdivo*) (Bristol-Myers Squibb Pharmaceutical Limited)	For treating advanced (unresectable or metastatic) melanoma	RED Approved for use within the *Lincolnshire Joint Formulary*.
Olaparib 50mg capsules (Lynparza) (AstraZeneca UK Ltd)	For maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum based chemotherapy	RED Approved for use within the *Lincolnshire Joint Formulary*
Panobinostat 10mg, 15mg and 20mg capsules (*Farydak*) (Novartis Pharmaceuticals UK Ltd)	For treating multiple myeloma after at least two previous treatments	RED Approved for inclusion in the *Lincolnshire Joint Formulary*.
Radium 223 dichloride (*Xofigo*) 1000 kBq/mL solution for injection.(Bayer)	For treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases.	Designated RED for these indications. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Ramucirumab 10mg/ml solution for infusion (*Cyramza*) (Eli Lilly and Company Ltd)	For treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*.
Salmeterol 50microgram/ fluticasone propionate 500 microgram per actuation dry powder inhaler (*AirFluSal Forspiro*) (Sandoz ltd)	For the symptomatic treatment of adults with Chronic Obstructive Pulmonary Disease (COPD), specifically those with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations who have significant symptoms despite regular bronchodilator therapy.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*.
Trametinib 0.5mg and 2mg tablets (*Mekinist*) (Novartis Pharmaceuticals UK Ltd)	For use as monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Vortioxetine 5mg, 10mg and 20mg tablets (*Brintellix*) (Lundbeck Ltd)	For the treatment of major depressive episodes in adults.	Designation: AMBER without shared care. Third line. Approved for inclusion in the *Lincolnshire 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 PACEF website (http://lincolnshire-pacef.nhs.uk). 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

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.

GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

RAPID DRUG ASSESSMENT: *SALMETEROL 50 MICROGRAM/FLUTICASONE PROPIONATE 500 MICROGRAM PER ACTUATION DRY POWDER INHALER (AIRFLUSAL FORSPIRO)*

***AirFluSal Forspiro 50/500* is a new salmeterol/fluticasone combination dry powder inhaler licensed for the treatment of COPD in adults. Comparative evidence suggests equivalent efficacy and safety to the *Seretide Accuhaler 500*; *AirFluSal Forspiro* is also lower cost. *AirFluSal Forspiro 50/500* is designated GREEN and preferred for new patients; therapeutic switching is advocated as part of the 2016/17 QIPP Programme.**

AirFluSal Forspiro is a new lower cost combination salmeterol/fluticasone dry powder inhaler. At present, it is solely indicated for the symptomatic treatment of adults with Chronic Obstructive Pulmonary Disease (COPD), specifically those with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations who have significant symptoms despite regular bronchodilator therapy. A marketing authorisation for use in the treatment of asthma has been applied for, but has not yet been approved. *AirFluSal Forspiro* is only intended for use by adults (i.e. those aged 18 years and older).

For *AirFluSal Forspiro* to obtain a UK marketing authorisation, bioequivalence had to be demonstrated against the originator device, *Seretide Accuhaler*. In a randomised equivalence trial, *AirFluSal Forspiro* (100mcg/50mcg or 500mcg/50mcg) was compared to the equivalent strength of *Seretide Accuhaler* (100mcg/50mcg or 500mcg/50mcg). The object of the trial was to compare efficacy and safety in 555 patients aged between 12 and 65 years of age with moderate to severe persistent asthma. Patients were randomised to either *AirFluSal Forspiro* or Seretide Accuhaler for at least 6 months and had to be using either an inhaled corticosteroid (ICS) or an inhaled ICS plus long acting beta agonist (LABA) combination product over 6 months prior to induction into the trial. Measured in terms of change in forced expiratory volume in 1 second (FEV_1) and other markers of respiratory function, results demonstrated that *AirFluSal Forspiro* was comparable and non-inferior to *Seretide Accuhaler* at both of the doses investigated.

PACEF were concerned that comparative evidence between the two devices was only available in patients suffering from asthma, currently a non-licensed indication. According to European Medicines Agency guidelines, evidence of therapeutic equivalence for once product compared to an originator brand only needs to be available in one relevant population.

In terms of the suitability of the device, in a small 28 day user handling study conducted in 24 patients, the *Forspiro* device was deemed to be very easy or fairly easy to use by the vast majority of participants, even in the no instruction group.

A cost comparison reveals that *AirFluSal Forspiro* is priced 20% lower than the *Seretide Accuhaler*:

Drug	Indication(s)	Daily dose	Cost (£) (doses)
***AirFluSal Forspiro 50/500* (salmeterol 50 microgram/ fluticasone propionate 500 micrograms) inhalation powder (Sandoz Ltd)**	**For the symptomatic treatment of adults with Chronic Obstructive Pulmonary Disease**	**One inhalation twice daily**	**£32.74 (60)**

	(COPD), specifically those with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations who have significant symptoms despite regular bronchodilator therapy.		
Seretide Accuhaler 500 (salmeterol 50 microgram/ fluticasone propionate 500 micrograms) (GlaxoSmithKline UK Ltd)	For the regular treatment of asthma where use of a combination product (long- acting β_2 agonist and inhaled corticosteroid) is appropriate. For the symptomatic treatment of patients with COPD, with a FEV_1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.	One inhalation twice daily	£40.92 (60)

Estimated annual savings by CCG assuming 100% switching from *Seretide Accuhaler 500* to *AirFluSal Forspiro* are:

	Estimated Annual Saving (assuming 100% switching)
Lincolnshire East CCG	£92,074
Lincolnshire West CCG	£53,072
South Lincolnshire CCG	£34,323
South West Lincolnshire CCG	£24,507
Liincolnshire	£203,976

On the basis that 67-78% of *Seretide Accuhaler 500* is prescribed for COPD, it is expected that half to two-thirds of patients currently managed on *Seretide Accuhaler 500* could be managed as well on the lower cost *AirFluSal Forspiro* product.

PACEF Recommendation:
Following review of the comparative evidence and inspection of the two devices, PACEF are satisfied as to the equivalence of the *AirFluSal Forspiro 50/500* and the *Seretide Accuhaler 500* products. As a result of this, *AirFluSal Forspiro 50/500* is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*. Prescribers are reminded that *AirFluSal Forspiro 50/500* only holds a marketing authorisation for the treatment of adults with COPD, but not asthma. Our

understanding is that the manufacturer has submitted an application for an asthma license based on the evidence detailed above, but that this has not yet been approved. Prescribers are encouraged to use *AirFluSal Forspiro 50/500* as the first line salmeterol 50 microgram/ fluticasone propionate 500 micrograms product of choice within the terms of its marketing authorisation. On the basis that 67-78% of *Seretide Accuhaler 500* is prescribed for COPD, it is expected that half to two-thirds of patients currently managed on *Seretide Accuhaler 500* could be managed as well on the lower cost *AirFluSal Forspiro* product. As a result of this, switches from *Seretide Accuhaler* 500 to *AirFluSal Forspiro* are included in the QIPP Programme for 2016/17 and will be promoted to practices by prescribing advisers; a switch protocol is in development and technician support will be available to practices wishing to undertake this switch. Sandoz have also produced a range of supporting materials including an online video, a smart phone app and a patient information leaflet. Prescribers are reminded that fluticasone is not the first line recommended ICS in COPD due to the increased risk of pneumonia compared to alternative inhaled steroids.

RAPID DRUG ASSESSMENT: *BECLOMETASONE DIPROPIONATE 200MICROGRAM/FORMOTEROL 6MICROGRAM PER ACTUATION (FOSTAIR 200/6) METERED DOSE INHALER AND NEXTHALER*

Fostair 200/6* metered dose inhaler and *Fostair 200/6 NEXThaler* are approved for use as cost-effective alternatives to higher cost equivalent products such as *Seretide Evohaler 250/25*, *Seretide Accuhaler 500* and *Symbicort Turbohaler 400/12.

The newly launched *Fostair 200/6* metered dose inhaler and *NEXThaler* contain beclometasone 200 micrograms (as beclometasone dipropionate) and 6 micrograms of formoterol fumarate dehydrate per actuation. Beclometasone dipropionate in *Fostair* is delivered as extrafine particles resulting in a more potent effect than formulations of beclometasone dipropionate with non-extra fine particle size distribution. For example, 100 micrograms of beclometasone dipropionate extrafine in *Fostair* is equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation

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This new higher strength version of *Fostair* is licensed for the treatment of adult asthma (18 years of age and over) where the use of a combination ICS/LABA is considered appropriate (i.e. in patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta2-agonist or in patients already adequately controlled on both ICS and LABA). *Fostair 200/6* pMDI and *NEXThaler* are not indicated for the treatment of acute asthma attacks or for maintenance and reliever therapy (MART). The manufacturer (Chiesi) has confirmed that there are no imminent plans to apply for a marketing authorisation for the treatment of COPD.

Supporting evidence comes from a small 12 week head to head trial against an alternative licensed extra fine particle formulation of beclomethasone (*Qvar*). *Fostair 200/6* demonstrated superiority in terms of improved peak expiratory flow (PEF) and a number of secondary outcomes demonstrating improved symptom control of asthma.

Lower strength formulations of *Fostair* in both the MDI and *NEXThale*r devices are already available through the *Lincolnshire Joint Formulary.*

A cost comparison between *Fostair 200/6* MDI and 200/6 *NEXThaler* and comparable higher dose ICS/LABA preparations reveals that *Fostair 200/6* is always the lowest cost product, even compared to low cost alternatives such as *Sirdupla 250/25* MDI and *DuoResp Spiromax 320/9.*

Metered Dose Inhalers (MDIs): *30 day cost of high dose combination pMDI inhalers (high dose >1000 mcg beclometasone (BDP)*

Drug	**Indication(s)**	**Dose**	**Cost (£) 30 days**
***Fostair 200/6* MDI (beclometasone 200 micrograms (as beclometasone dipropionate) and 6 micrograms of formoterol fumarate dehydrate) metered dose inhaler (Chiesi Ltd)**	**For the regular treatment of asthma in adults) where the use of a combination ICS/LABA is considered appropriate (i.e. in patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta2-agonist or in patients already adequately controlled on both ICS and LABA).**	**2 puffs twice daily**	**£29.32 (120 doses)**
Seretide Evohaler 250/25 (fluticasone propionate 250 micrograms and 25micrograms of salmeterol xinafoate) metered dose inhaler (GlaxoSmith Kline UK Ltd)	For the regular treatment of asthma where use of a combination product (long-acting β_2 agonist and inhaled corticosteroid) is appropriate	2 puffs twice daily	£59.48 (120 doses)
Sirdupla 250/25 (fluticasone propionate 250mcg/ salmeterol 25mcg metered dose inhaler (*Sirdupla*) (Mylan)	For the regular treatment of asthma where combination long acting β2-agonist and inhaled corticosteroid therapy is appropriate.	2 puffs twice daily	£44.61 (120 doses)
Flutiform 250/10 (fluticasone propionate 250 micrograms and 10micrograms of formoterol fumarate dihydrate) metered dose inhaler (Napp Pharmaceuticals Ltd)	For the regular treatment of asthma in adults where the use of a combination product (an inhaled corticosteroid and a long-acting β_2 agonist) is appropriate.	2 puffs twice daily	£45.56 (120 doses)

Dry powder devices: 30 day cost of high dose combination DPI inhalers (high dose >1000 mcg BDP)

Drug	Indication(s)	Dose	Cost (£) (doses)
Fostair 200/6 NEXThaler **(beclometasone 200 micrograms (as beclometasone dipropionate) and 6 micrograms of formoterol fumarate dehydrate) (Chiesi Ltd)**	**For the regular treatment of asthma in adults where the use of a combination ICS/LABA is considered appropriate (i.e. in patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta2-agonist or in patients already adequately controlled on both ICS and LABA).**	**2 puffs twice daily**	**£29.32 (120 doses)**
Seretide Accuhaler 500 (salmeterol 50 microgram/ fluticasone propionate 500 micrograms) (GlaxoSmithKline UK Ltd)	For the regular treatment of asthma where use of a combination product (long-acting β_2 agonist and inhaled corticosteroid) is appropriate. For the symptomatic treatment of patients with COPD, with a FEV_1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.	1 puff twice daily	£40.92 (60 doses)
Symbicort Turbohaler 400/12 (budesonide 400microgram/formoterol fumarate dihydrate 12microgram) (AstraZeneca UK Ltd)	For the regular treatment of asthma where use of a combination (inhaled	2 puffs twice daily	£76.00 (2x60 doses)

	corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate. For the symptomatic treatment of patients with COPD with FEV_1 <70% predicted normal (post bronchodilator) and an exacerbation history despite regular bronchodilator therapy.		
DuoResp Spiromax 320/9 (budesonide 400microgram/formoterol fumarate dihydrate 12microgram) (Teva UK Ltd)	Inhaled corticosteroid/'long acting bronchodilator combination dry powder inhaler for the regular treatment of asthma and the symptomatic treatment of severe COPD with a history of repeated exacerbations despite regular therapy with long-acting bronchodilators.	2 puffs twice daily	£59.94 (2x60 doses)

PACEF Recommendation:
Lower strengths of *Fostair MDI* and *Fostair NEXThaler* are already available on the *LincoInshire Joint Formulary*, designation GREEN. *Fostair 200/6 MDI* and *200/6 NEXThaler* offer a cost-effective alternative to a number of higher dose ICS/LABA combination MDIs and dry powder devices (see cost comparison). Those practices not currently engaged in a switch from *Seretide Evohaler 250/25* to *Sirdupla MDI* or *Symbicort Turbohaler 400/12* to *DuoResp Spiromax* 320/9 may wish to consider switching to *Fostair 200/6 MDI* or *Fostair 200/6 NEXThaler* as an alternative option. Both *Fostair 200/6 MDI* and *Fostair 200/6 NEXThaler* are designated GREEN and approved for use on the *LincoInshire Joint Formulary*.

SUPPLY DIFFICULTIES WITH AMIODARINE AND FLECAINIDE

Supply problems are beginning to emerge around two specialist cardiovascular medicines:

- Amiodarone 100mg and 200mg tablets
- Flecainide acetate 50mg and 100mg tablets.

At present, amiodarone remains available, but with only one manufacturer producing the product, the supply chain is fragile.

In terms of flecainide, ULH Cardiology has identified propafenone 150mg and 300mg tablets as the preferred alternative.

As both amiodarone and flecainide are designated AMBER, changes of therapy should not be implemented without specialist advice and support.

SHARED CARE GUIDELINES

PACEF have reviewed, updated and approved the following shared care guidelines:

- *Somatropin for growth deficiencies in adults*
- *Cinacalcet in the management of secondary hyperparathyroidism in adults*

These SCGs are now available through the PACEF website or by contacting Cathy Johnson at cathy.johnson@ardengemcsu.nhs.uk

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (FEBRUARY 2016)

Valproate and risk of abnormal pregnancy outcomes: New communication materials

New resources have been launched to highlight the risk of developmental disorders and congenital malformations in children exposed to valproate in utero. Hard copies of these resources were sent out to all healthcare professionals during February.

They include:

(1) A Booklet for Healthcare Professionals

This gives a comprehensive overview of the risks of valproate in females of childbearing potential and during pregnancy and details points to remember when considering initiation of valproate in women of childbearing potential or girls.

(2) Consultation checklist

This enables the healthcare professional to check they have provided the women/girl with all the necessary information and that she has fully understood it. It is suggested that the completed checklist is added to the patient's medical records as a permanent record of the discussion.

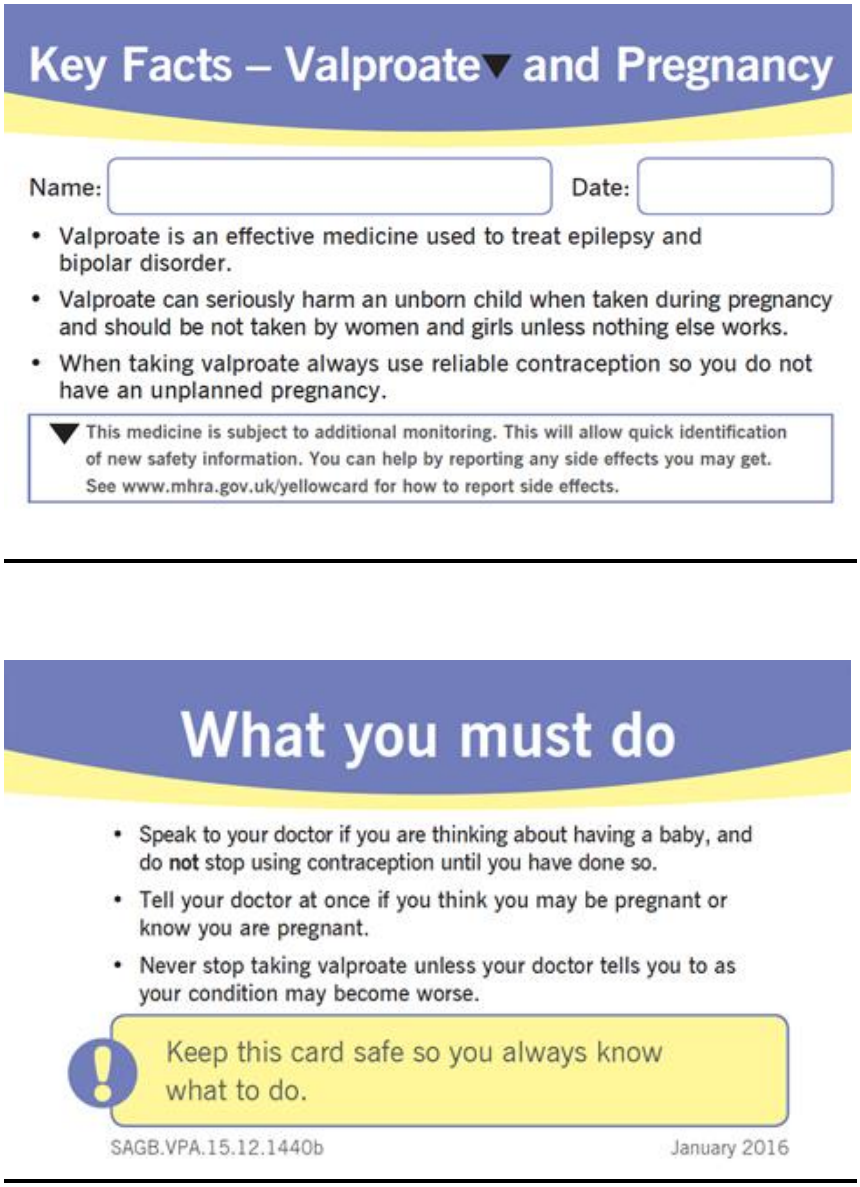
(3) Patient Guide

When considering treating a woman of childbearing potential or a girl with valproate, they or their carer should be provided with the valproate patient guide and steps should be taken to ensure that they understand the information it contains. Paediatricians should also refer parents or carers to the information about valproate from the Royal College of Paediatrics and Child Health.

(4) Patient Card

When a medicine related to valproate is dispensed for a woman of childbearing potential or a girl, a patient card should be provided unless the patient or carer confirms that they already have one.

An example of the card is reproduced below:



Key Facts – Valproate▼ and Pregnancy

Name: Date:

- Valproate is an effective medicine used to treat epilepsy and bipolar disorder.
- Valproate can seriously harm an unborn child when taken during pregnancy and should be not taken by women and girls unless nothing else works.
- When taking valproate always use reliable contraception so you do not have an unplanned pregnancy.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See www.mhra.gov.uk/yellowcard for how to report side effects.

What you must do

- Speak to your doctor if you are thinking about having a baby, and do **not** stop using contraception until you have done so.
- Tell your doctor at once if you think you may be pregnant or know you are pregnant.
- Never stop taking valproate unless your doctor tells you to as your condition may become worse.

Keep this card safe so you always know what to do.

SAGB.VPA.15.12.1440b January 2016

Patients should be encouraged to enter their name and date in the space provided, to reinforce their own accountability to consider the information it contains. Managers of dispensing services are being asked to ensure that processes are in place to allow these requirements to be met.

(5) Changes to packaging

Later in 2016, the outer packaging for medicines containing valproate will include a warning for women on the risk of adverse pregnancy outcomes.

Further advice has been issued to general practitioners and pharmacists.

For general practitioners:

- Valproate treatment must be started and supervised by a specialist experienced in managing epilepsy or bipolar disorder.
- Consider the need to arrange treatment reviews with the relevant specialist for women of childbearing potential and girls who are currently taking valproate.

- If a woman who is taking valproate tells you she is pregnant or would like to have a baby, refer her to the specialist responsible for her care.
- Report any suspected side effects to valproate or any other medicine on a Yellow Card.

For pharmacists

- All women of childbearing potential or girls receiving a dispensed supply of valproate should be given a patient card, unless already in possession of one.
- The patient should be encouraged to read the card and enter her name and date to reinforce her own accountability to consider the information it contains.
- Report any suspected side effects to valproate or any other medicine on a Yellow Card.

Off-label use: risks and advice still apply

Valproate is not licensed for treatment of conditions other than epilepsy or bipolar disorder in the UK. However, valproate containing products are sometimes used 'off-label' (e.g. for migraine or chronic pain). The same guidance and risks apply to the use of valproate whatever the indication..

Spironolactone and renin-angiotensin system drugs and risk of potentially fatal hyperkalaemia in heart failure

Monitoring of blood electrolytes is essential in patients co-prescribed a potassium-sparing diuretic and an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) for heart failure. Concomitant use of spironolactone with an ACEI or ARB is not routinely recommended because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment.

Spironolactone is indicated in patients with congestive heart failure. It is a competitive aldosterone antagonist that increases sodium excretion while reducing potassium loss at the distal renal tubule. This mechanism of action means that hyperkalaemia can occur, particularly in patients with impaired renal function. Spironolactone should not be used in patients with severe renal impairment or pre-existing hyperkalaemia.

ACEIs are mainly indicated in patients with hypertension or heart failure. ARBs are also indicated in hypertension and some are also indicated in heart failure. Recognised side effects of treatment with an ACEI or ARB include renal dysfunction and an increase in serum potassium. Risk factors for hyperkalaemia, such as renal insufficiency and diabetes mellitus, are more common in patients who require treatment with ACEI or ARB. Dehydration may also increase the risk of renal dysfunction leading to hyperkalaemia. Hyperkalaemia has been estimated to occur in between 1 in 100 and 1 in 1000 patients who take an ACEI or ARB.

Reminder for healthcare professionals:

- Concomitant use of spironolactone with an ACEI or ARB is not routinely recommended because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment.
- Use the lowest effective dose of spironolactone and ACEI or ARB if co-administration is considered essential.
- Regularly monitor serum potassium levels and renal function .I
- Interrupt or discontinue treatment in the event of hyperkalaemia
- Report any suspected adverse reactions on a Yellow Card.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (MARCH 2016)

Trametinib (*Mekinist*): Risk of gastrointestinal perforation and colitis

Use trametinib, authorised either as monotherapy or combined with dabrafenib, with caution in patients with risk factors for gastrointestinal perforation.

A review by EU medicines regulators has concluded that trametinib can cause gastrointestinal perforation or colitis.

Advice for healthcare professionals:

- Use trametinib, authorised either as monotherapy or combined with dabrafenib, with caution in patients with risk factors for gastrointestinal perforation, such as gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation
- In these patients, be vigilant for signs and symptoms of gastrointestinal perforation. Patients should be advised to seek urgent medical attention if they develop severe abdominal pain
- Suspected adverse reactions to trametinib should be reported to us on a Yellow Card
- Trametinib (*Mekinist*), authorised as monotherapy or combined with dabrafenib, is indicated for the treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation.

NICE UPDATE

NICE Technology Appraisal	Guidance	PACEF Recommendation
NICE TA 367: *Vortioxetine for treating major depressive episodes* (November 2015)	Vortioxetine (*Brintellix*) is recommended as a possible treatment for adults having a first or recurrent major depressive episode, if the current episode has not responded to two antidepressants.	Vortioxetine 5mg, 10mg and 20mg tablets (*Brintellix*) are approved for third line use. Designation: AMBER without shared care. The first two monthly prescriptions will be issued by specialist mental health services with the prospect of ongoing GP prescribing in those that respond. Approved for inclusion in the *Lincolnshire Joint Formulary*
NICE TA375 *Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed* (January 2016)	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis. Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance.	All of these products are designated RED for this indication and included in the *Lincolnshire Joint Formulary*.

NICE TA376 *Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases* (January 2016)	Radium-223 dichloride is recommended as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases.	Radium 223 dichloride (*Xofigo*) 1000 kBq/mL solution for injection is designated RED for this indication and approved for inclusion in the *Lincolnshire Joint Formulary.*
NICE TA377 *Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated* (January 2016)	Enzalutamide is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people who have no/or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated.	Enzalutamide 40mg capsules (*Xtandi*) are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary*.
NICE TA378 *Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy* (January 2016)	Ramucirumab alone or with paclitaxel is not re-commended for advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy.	Ramucirumab 10mg/ml solution for infusion (*Cyramza*) is designated RED-RED for this indication and is not approved for inclusion in the *Lincolnshire Joint Formulary.*
NICE TA379 *Nintedanib for treating idiopathic pulmonary fibrosis* (January 2016)	Nintedanib is recommended as an option for treating idiopathic pulmonary fibrosis, only if: the person has a forced vital capacity (FVC) between 50% and 80% of predicted and treatment is stopped if disease progresses in any 12-month period.	Nintedanib 100mg and 150mg capsules (*Ofev*) are designated RED for this indication. Likely to be prescribed within tertiary centres only. Approved for use within the *Lincolnshire Joint Formulary.*
NICE TA380 *Panobinostat for treating multiple myeloma after at least two previous treatments* (January 2016)	Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation as an option for adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immuno-modulatory agent.	Panobinostat 10mg, 15mg and 20mg capsules (Farydak) are designated RED for this indication. Approved for use within the *Lincolnshire Joint Formulary.*
NICE TA381 *Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum based chemotherapy* (January 2016)	Olaparib is recommended as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum based chemotherapy.	Olaparib 50mg capsules (Lynparza) are designated RED for this indication. Approved for use within the *Lincolnshire Joint Formulary.*
NICE TA382 *Eltrombopag for treating severe aplastic anaemia refractory to immunosuppressive therapy (terminated appraisal)* (January 2016)	NICE is unable to make a recommendation about the use in the NHS of eltrombopag for treating severe aplastic anaemia refractory to immunosuppressive therapy because no evidence submission was received from Novartis for the technology.	Eltrombopag 25mg and 50mg tablets (Revolade) are designated RED-RED for this indication. Not approved for inclusion in the *Lincolnshire Joint Formulary.*

NICE TA383 *TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis* (February 2016)	Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product.	All of these products are designated RED for this indication and included in the *Lincolnshire Joint Formulary*.
NICE TA384 *Nivolumab for treating advanced (unresectable or metastatic) melanoma* (February 2016)	Nivolumab as monotherapy is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults.	Nivolumab 10mg/ml concentrate for solution for infusion (*Opdivo*) is designated RED for this indication. Approved for use within the *Lincolnshire Joint Formulary.*

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