NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 2 **January 2013**

What's new this month?

- **Prescribers are strongly advised not to pre-empt the launch of the national shingles vaccination programme by offering varicella zoster virus vaccine (*Zostavax*) on the NHS before the national vaccination programme is in place. The Joint Committee on Vaccination and Immunisation (JCVI) has real concerns over the cost-effectiveness of the vaccine and is working to ensure that the national programme benefits from targeting at a specific patient group and secures the vaccine at an affordable price. As a result of this varicella zoster virus vaccine (*Zostavax*) continues to be designated RED-RED; it should not be prescribed on NHS prescription, although appropriate patients can be prescribed for privately (see page 3).**
- **Fidaxomicin (*Difficlir*) is a new antibiotic indicated for the treatment of *Clostridium difficile* infection (CDI) in adults. It is designated RED and should only be initiated on the advice of a microbiologist for patients experiencing first CDI recurrence after an apparently resolved initial case. The full 10 day course will be prescribed within secondary care and there will be no need for GPs to prescribe (see page 4).**
- **Doxycycline 40mg modified release capsules (*Efracea*) for the treatment of facial rosacea have been re-assessed and continue to be designated RED-RED (see page 5).**
- **Ulipristal acetate (*Esmya*) offers a genuine alternative option for women requiring pre-operative treatment for the moderate to severe symptoms of uterine fibroids and is designated AMBER. The product is more expensive than the alternative injectable gonadorelin analogues, but is of comparable efficacy and may be better tolerated in terms of frequency of hot flushes (see page 6).**
- **Aclidinium bromide dry powder inhaler (*Eklira Genuair*) has been designated GREEN for the maintenance treatment of COPD. Where a LAMA is indicated, tiotropium should be used first line; where the patient is intolerant of tiotropium or experiences problems with the *Handihaler* or *Respimat* devices, aclidinium bromide (*Eklira Genuair*) may be considered as an alternative. Despite the cost differential in favour of aclidinium bromide, prescribers are not encouraged to undertake product switching to the lower cost product (see page 7).**
- **In view of mounting safety concerns, tiotropium bromide (*Spiriva Respimat*) is designated RED-RED and should no longer be initiated in new patients; all new initiations of tiotropium should be for the *Handihaler* device. All existing patients continuing to use the *Respimat* device need to be reviewed and alternatives considered (see page 9).**
- **Fluticasone/formoterol (*Flutiform*) MDI is a new ICS/LABA combination inhaler for the treatment of asthma: it has been designated GREEN. Despite the cost differential in favour of *Flutiform* over *Seretide Evohaler* at the higher strengths, prescribers are not encouraged to undertake product switching to the lower cost product (see page 9)**

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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 Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: *NOVEMBER/DECEMBER 2012 UPDATE*

Drug	Indication(s)	Traffic Light Status
Abiraterone acetate 250mg tablets (*Zytiga*)	For the treatment of metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel containing chemotherapy regimen.	RED
Aclidinium bromide dry powder inhaler (*Eklira Genuair*)	For the maintenance treatment of chronic obstructive pulmonary disease (COPD).	GREEN
Agomelatine 25mg tablets (Valdoxan)	Licensed for the treatment of major depressive episodes in adults.	RED
Doxycycline 40mg modified release capsules (MR) (*Efracea*)	For the treatment of facial rosacea	RED-RED
Erlotinib 150mg tablets (*Tarceva*)	For the treatment of non-small cell lung cancer	RED
Fidaxomicin 200mg tablets (*Dificlir*)	For the treatment of *Clostridium difficile* infection in adults.	RED For initiation by consultant microbiologists only for adults experiencing first CDI recurrence

		after an apparently resolved initial case. Full courses are to be prescribed from within secondary care.
Fluticasone/formoterol (*Flutiform*) MDI 50mcg/5mcg, 125/5 and 250/10	For the regular treatment of asthma where long acting beta 2 agonist and inhaled corticosteroid is appropriate	GREEN
Lapatinib tablets 250mg (*Tyverb*)	For use in combination with an aromatase inhibitor for postmenopausal hormone receptor-positive HER2 positive metastatic breast cancer not currently intended for chemotherapy and not previously treated with trastuzumab or an aromatase inhibitor.	RED-RED
Tiotropium bromide (*Spiriva Handihaler*) 18microgram capsule plus device	For the maintenance treatment of COPD.	GREEN
Tiotropium bromide (*Spiriva Respimat*) 2.5microgram per dose	For the maintenance treatment of COPD.	RED-RED
Ulipristal acetate 5mg tablets (*Esmya*)	For the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.	AMBER
Varicella zoster vaccine (Zostavax)	Licensed for the prevention of herpes zoster (or shingles) and herpes zoster-related post-herpetic neuralgia (PHN) in adults 50 years of age or older	RED-RED GPs can privately prescribe but cannot supply; patients must expect to pay for the vaccine (including an additional dispensing fee) at their local community pharmacy. GPs can administer the vaccine free of charge as part of their NHS work.

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.**

REVIEW: *VARICELLA ZOSTER VIRUS VACCINE (ZOSTAVAX)*

This is an update of the original review of this product that appeared in *PACE Bulletin* Vol 6 No 10 (July 2012)

Zostavax is a varicella zoster virus vaccine licensed for the prevention of herpes zoster (shingles) and herpes zoster related post-herpetic neuralgia in patients aged 50 years of age and older. The Department of Heath has referred the product to the Joint Committee on Vaccination and Immunisation (JCVI) who have recommended that a national shingles vaccination programme should be introduced for people aged from 70 up to and including 79 years conditional on (1) the vaccine becoming available at a cost-effective price and (2) security of supply being maintained. A final announcement of the national programme by the DoH is expected imminently; such a programme is not expected to launch until later in 2013. In the meantime, varicella zoster virus vaccine (*Zostavax*) should not be prescribed on the NHS in Lincolnshire under any circumstances. For patients unable to wait for the national programme or those outside of the age range of the planned programme, GPs can privately prescribe but cannot supply; patients must expect to pay for the vaccine (including an additional dispensing fee) at their local

community pharmacy. GPs can administer the vaccine free of charge as part of their NHS work.

PACEF Recommendation:
Prescribers are strongly advised not to pre-empt the launch of the national shingles vaccination programme by offering varicella zoster virus vaccine (*Zostavax*) on the NHS before the national programme is in place. The JCVI has real concerns over the cost-effectiveness of the vaccine and is working to ensure that the national programme benefits from targeting at a specific patient group and secures the vaccine at an affordable price. As a result of this varicella zoster virus vaccine (*Zostavax*) continues to be designated RED-RED; it should not be prescribed on NHS prescription, although appropriate patients can be prescribed for privately.

NEW DRUG ASSESSMENT: *FIDAXOMICIN 200MG TABLETS* (*DIFICLIR*)

Fidaxomicin (*Dificlir*) is the first in a new class of macrocyclic antibiotics. It has a narrow spectrum of antibacterial activity mainly directed against *Clostridium difficile,* but exerts moderate activity against some other Gram-positive microorganisms. It is very poorly absorbed systemically and exerts its activity in the gastrointestinal tract. It is licensed for use in adults for the treatment of *Clostridium difficile* infections (CDI) (also known as *C. difficile*-associated diarrhoea (CDAD)).

The evidence for fidaxomicin comes from two multi-centred, double-blind randomised controlled trials which compared fidaxomicin with vancomycin. In both studies fidaxomicin was found to be non-inferior to vancomycin with regard to clinical cure; however recurrence rates were significantly lower and sustained response significantly higher in the fidaxomicin groups. There are no trials comparing fidaxomicin with metronidazole.

The standard dose of fidaxomicin is 200mg twice daily for 10 days. A cost comparison with oral vancomycin reveals the following:

	Treatment dose for CDI	Cost per course
Fidaxomicin 200mg tablets (*Dificlir*)	200mg twice daily for 10 days	£1,350
Metronidazole 400mg or 500mg tablets (generic)	400mg or 500mg every eight hours for 10 to 14 days	£2.48 (400mg tds for 14 days) £68.28 (500mg tds for 14 days)
Vancomycin 125mg or 250mg capsules (generic)	125mg every 6 hours for 10 to 14 days (increased up to 500mg every 6 hours if infection fails to respond or is life threatening)	£264.94 (125mg qds for 14 days) £264.94 (250mg qds for 14 days) £529.88 (500mg qds for 14 days)

PACEF Recommendation:
PACEF recognise that the effective treatment of CDI is becoming increasing problematic and that any new antibiotic that can potentially add to the rather limited range of effective treatment options available to the microbiologist needs serious consideration. Comparative trials suggest that fidaxomicin is non-inferior to standard therapy, but with significantly lower recurrence rates. However, it is significantly higher in cost. After consideration of all these factors, fidaxomicin (*Difliclir*) is designated RED. It should be initiated solely on

the advice of a microbiologist and restricted to use in adults experiencing first CDI recurrence after an apparently resolved initial case. The full 10 day course will be prescribed within secondary care and there will be no need for GPs to prescribe. Any requests to GPs to prescribe fidaxomicin within this context should be referred back to the initiating specialist.

UPDATED NEW DRUG ASSESSMENT: *DOXYCYCLINE 40MG MODIFIED RELEASE CAPSULE (EFRACEA)*

This is an updated version of an assessment of doxycycline 40mg MR capsules (*Efracea*) that originally appeared in *PACE Bulletin* Vol 4 No 9 (June 2010)

Doxycycline 40mg modified release (MR) (*Efracea*) is the first doxycycline formulation with a marketing authorisation for the treatment of adult patients with facial rosacea. Whilst doxycycline has been a recognised treatment for this condition for some time, none of the previously existing preparations are licensed for this purpose. Conventionally, doxycycline 100mg daily, a systemic antibacterial dose, has been prescribed for moderately severe acne. Doxycycline 40mg MR capsules (*Efracea*) contain a sub-antimicrobial dose of doxycycline which, nonetheless, appears to have anti-inflammatory properties. As the dose of doxycycline used is below that required for its antimicrobial effect, chronic use should not be associated with increasing risk of intestinal bacterial resistance. No incidents were reported in clinical trials but the manufacturers state that the risk of this developing cannot be excluded.

Clinical evidence from two 16 week placebo controlled randomized controlled trials (RCTs) demonstrate a reduction in the number of lesions with active treatment and no effect on other symptoms such as the incidence of nodules and the extent and severity of erythema. *Efracea* emerges from these trials with evidence of superiority to placebo, but comparative trials against other alternative treatments (including alternative tetracycline doses and formulations) are still lacking.

A Cochrane review in 2011 looked at a range of effective and evidence-based management strategies for rosacea. 58 RCTs were identified covering a range of different therapies including topical metronidazole, oral antibiotics, topical azelaic cream or gel, topical benzoyl peroxide and/or combined with topical antibiotics, sulphacetamide/sulphur and others. The majority of the trials identified were assessed as being at high or unclear risk of bias. However, there was some evidence to support the effectiveness of topical metronidazole, azelaic acid and doxycycline 40mg in the treatment of moderate to severe rosacea. There was no statistically significant difference in effectiveness between doxycycline 40mg and 100mg but there were fewer adverse effects associated with the 40mg strength.

The ORCA (Oracea for Rosacea) trial was a company-sponsored open-label, community-based, 12-week assessment of the effectiveness and safety of doxycycline 40mg in patients who would otherwise have been treated with antibiotic-dose doxycycline. 1196 patients took doxycycline 40mg daily for 12 weeks and investigators evaluated each patient's rosacea severity and erythema at baseline and at weeks 2, 4, 8 and 12. The primary outcome measure was the change in investigator global assessment score of rosacea severity from baseline to end point (week 12). By the end of the study, 35.5% of participants had clear and 39.1% had near clear scores. Direct comparative data with doxycycline 100mg is still lacking.

A cost comparison of doxycycline 40mg modified release (Efracea) with other alternative treatments reveals the following:

	Dose	Cost (28 days)
Doxycycline 40mg modified release capsules (MR) (*Efracea*)	40mg once daily	£14.89
Doxycycline 100mg capsules (generic)	100mg once daily	£1.65
Lymecycline 408mg capsules (*Tetralysal 300*)	408mg once daily	£7.77
Oxytetracycline 250mg tablets	500mg twice daily	£4.96

PACEF Recommendation:
Trial evidence supporting the use of doxycycline 40mg modified release capsules (*Efracea*) remains limited with no comparative trials against established alternatives such as doxycycline capsules 100mg. In the absence of such evidence, PACEF remain unconvinced that any additional benefits are commensurate with the increased cost. As a result of this, doxycycline 40mg modified release capsules (Efracea) continue to be designated RED-RED.

NEW DRUG ASSESSMENT: *ULIPRISTAL ACETATE 5MG TABLETS (ESMYA)*

Ulipristal acetate is a selective progesterone receptor modulator which reduces fibroid volume by inhibiting cell proliferation and inducing programmed cell death (apoptosis). Ulipristal acetate 5mg tablets (*Esmya*) are indicated for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. One 5mg tablet is taken daily started on the first week of the menstrual cycle for up to 3 months.

PACEF assessed two randomised, parallel-group, double-blind, 13-week studies known as PEARL I and PEARL II. In PEARL I, 242 women with symptomatic fibroids planning to undergo surgery were randomized to ulipristal 5mg, 10mg or placebo each day. Treatment started during the first 4 days of menstruation and all patients received iron supplementation. Patients could have surgery after week 13 according to their clinical response, but no further pharmacologic treatment of fibroids was given. Menstrual bleeding was controlled in 91% of the 5mg group and 92% of the 10mg group, compared with 19% of the placebo group. Clinical and statistically significant reductions in uterine fibroid size were seen in both ulipristal groups compared with the placebo group. This study demonstrates the effectiveness of ulipristal compared to placebo and confirms 5mg daily as the optimum dose.

In PEARL II, 303 women with symptomatic fibroids planning to undergo surgery were randomized to treatment with 5mg or 10mg ulipristal daily plus an intramuscular saline injection once a month, or placebo tablets plus a 3.75mg leuprorelin acetate injection once a month. Treatment was started within 4 days after the start of the menstrual period and continued until week 13, when patients could have surgery. The primary endpoint was the proportion of patients with uterine bleeding at week 13 defined as a Pictorial Blood Loss Assessment Chart (PBAC) score <75 for the preceding 4 weeks. In the per-protocol population, similar proportions of patients in each group reached the primary endpoint, indicating non-inferiority for both doses of ulipristal in controlling bleeding. Moderate to severe hot flushes occurred in four times as many patients treated with leuprorelin than with ulipristal. No significant difference was seen between the ulipristal and leuprorelin groups in terms of

reporting of other adverse events. This study demonstrates the non-inferiority of ulipristal 5mg to monthly leuprorelin acetate injections and a possible advantage of ulipristal in terms of improved tolerability over leuprorelin. A subsequent superiority analysis showed that ulipristal 10mg was superior to leuprorelin in terms of efficacy although this is of limited relevance as only the 5mg strength is licensed in the UK.

A cost comparison between ulipristal and the injectable gonadorelin analogues currently in use reveals the following:

Drug	Dose	Cost (3 months)
Ulipristal acetate 5mg tablets (*Esmya*)	One 5mg tablet daily started on the first week of the menstrual cycle for up to 3 months.	£342.39
Leuprorelin acetate 3.75mg injection (*Prostap SR DCS*)	3.75mg as a single SC or IM injection given every month for 3 to 4 months	£225.72
Goserelin acetate 3.6mg injection (*Zoladex*)	3.6mg as a single SC injection given every month up to a maximum of 3 months	£195.00
Triptorelin acetate IM 3mg injection (*Decapeptyl SR*)	3mg every 4 weeks started during the first 5 days of the menstrual cycle for at least 3 months	£207.00
Triptorelin acetate IM 3.75mg injection (*Gonapeptyl Depot*)	3.75mg every 4 weeks started during the first 5 days of the menstrual cycle for at least 3 months	£245.07

PACEF Recommendation:
Following a review of the PEARL studies, PACEF are convinced that ulipristal acetate (*Esmya*) offers a genuine alternative option for women requiring pre-operative treatment for the moderate to severe symptoms of uterine fibroids. The product is more expensive than the alternative injectable gonadorelin analogues, but is of comparable efficacy and may be better tolerated in terms of frequency of hot flushes. The oral formulation may also make ulipristal more acceptable and convenient for some patients. As a result of this, ulipristal acetate 5mg tablets (*Esmya*) are designated AMBER.

NEW DRUG ASSESSMENT: *ACLIDINIUM BROMIDE BREATH ACTUATED DRY POWDER INHALER (EKLIRA GENUAIR)*

Aclidinium bromide (*Eklira Genuair*) is an inhaled twice-daily, long-acting antimuscarinic agent (LAMA) indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). Pre-clinical studies showed aclidinium to be a potent antagonist of human muscarinic receptors, with a long residence time at M_3 receptors and a shorter residence time at M_2 receptors, indicating the potential to provide sustained bronchodilation.

Clinical evidence is largely based on two placebo controlled trials of relatively short duration (24 weeks and 12 weeks) in a total of 1,385 patients with moderate to severe COPD. These trials show modest increases in pre-dose FEV1 (of the order of 100-140ml) over the trial period for the 400microgam (322 microgram) dose. Nonetheless this increase in FEV1 is in line with that seen with other long-acting

bronchodilators (both LABAs and LAMAs) including tiotropium. Incidence of antimuscarinic side-effects also appeared to be low. Both of these studies demonstrate the effectiveness and short-term safety of aclidinium in comparison to placebo in a defined group of patients.

In a third randomized, double-blind, double-dummy, crossover trial, 30 patients with moderate to severe COPD were given aclidinium 400 microgram (322 microgram) twice daily, tiotropium 18 microgram once daily or placebo for 15 days, with a 9 to 15 day washout between treatment periods. Treatments were administered through the *Genuair* or *HandiHaler* dry powder inhaler devices. This study is seriously flawed by its small population, short duration and the use of a non-validated questionnaire to assess night-time symptoms. However, the results suggest that twice-daily aclidinium *may* have similar efficacy to tiotropium, although much larger comparative trials of much longer duration would be required in order to confirm this.

In the absence of long-term safety data it is also not possible to fully assess the safety of aclidinium. This remains a concern as possible excess cardiovascular deaths have been attributed to other inhaled LAMAs (see later).

A cost comparison of all currently available long acting muscarinic antagonists (LAMAs) reveals the following:

Long acting muscarinic antagonists (LAMAs)

Drug	**Presentation**	**Dose**	**Cost per 30 days**
Aclidinium bromide	*Eklira Genuair* 400mcg (60D)	322 mcg twice daily	£28.60
Glycopyrronium bromide	*Seebri Breezhaler* capsules for use in inhaler 50mcg (30D)	44mcg once daily	£27.50
Tiotropium bromide	*Spiriva Handihaler* capsules for use in inhaler 18mcg (30D)	18mcg once daily	£34.87 (£33.50 refill)
Tiotropium bromide	*Spiriva Respimat* 2.5mcg (60D)	5mcg once daily	£35.50

PACEF Recommendation:
Very limited comparative trial evidence suggests that aclidinium bromide (*Eklira Genuair*) *may* have similar efficacy to tiotropium, although much larger comparative trials of much longer duration are required in order to confirm this. Nonetheless, PACEF recognise the need for an alternative LAMA to tiotropium bromide for patients unable to tolerate tiotropium and for those who experience difficulties with the various inhaler devices. Emerging safety issues around the use of the *Spiriva Respimat* device also further complicate treatment choice in this area (see later). Aclidinium bromide dry powder inhaler (*Eklira Genuair*) is designated GREEN for the maintenance treatment of COPD. Where a LAMA is indicated, tiotropium should be used first line; where the patient is intolerant of tiotropium or experiences problems with the *Handihaler* or *Respimat* devices, aclidinium bromide (*Eklira Genuair*) may be considered as an alternative. Despite the cost differential in favour of aclidinium bromide, prescribers are not encouraged to undertake product switching to the lower cost product as tiotropium remains the preferred LAMA for reasons detailed above. A forthcoming New Drug Assessment of another new LAMA, glycopyrronium bromide (*Seebri Breezhaler*), may necessitate further revision of this advice.

MOUNTING CONCERNS OVER THE SAFETY OF TIOTROPIUM BROMIDE (*SPIRIVA RESPIMAT*)

In the January 2011 issue of the *PACE Bulletin* (Vol 5 No1), we reported on the MHRA safety concerns related to the association between the *Spiriva Respimat* tiotropium inhaler and a non-significant increase in all-cause mortality compared to placebo. In response to this, PACEF decided to advocate the *Spiriva Handihaler* as the tiotropium inhaler device of choice on the basis that the *Handihaler* has actually been associated with a reduction in all cause mortality compared to placebo.

Following on from this, an editorial in the *British Medical Journal* published in November 2012 has called for the worldwide withdrawal of the tiotropium *Respimat* mist inhaler. The authors update the story beyond the systematic review and meta-analysis reported by the MHRA. In 2012, a Cochrane review of tiotropium versus placebo for COPD confirmed the significant increase in mortality for tiotropium *Respimat* and the differential risk between *Respimat* and *Handihaler* devices. Greater systemic exposure to tiotropium through the *Respimat* device is thought to increase the risk associated with the use of the *Respimat* device compared to the *Handihaler.* Another systematic review and meta-analysis has confirmed the increased risk of death with *Respimat* and identified the greatest risk as death from cardiovascular disease in patients with severe COPD taking a higher daily dose of tiotropium. The authors estimate that use of the *Respimat* device at a dose of 5 microgram for 12 months will cause one excess death for every 121 patients treated.

PACEF Recommendation:
In view of mounting safety concerns, tiotropium bromide (*Spiriva Respimat*) is designated RED-RED and should no longer be initiated in new patients; all new initiations of tiotropium should be for the *Handihaler* device. All existing patients continuing to use the *Respimat* device need to be reviewed and alternatives considered. In addition to the tiotropium *Handihaler*, two new LAMAs, aclidinium bromide (*Eklira Genuair*) (reviewed above) and glycopyrronium bromide (*Seebri Breezhaler*) (assessment coming soon), offer potential alternatives.

Reference:
Beasley R et al, Call for worldwide withdrawal of tiotropium Respimat mist inhaler, *BMJ* 2012; 345:e7390 doi: 10.1136/bmj.e7390 (published 9th November 2012)

NEW DRUG ASSESSMENT: *FLUTICASONE/FORMOTEROL METERED DOSE INHALER (FLUTIFORM)*

Flutiform is a combination inhaler containing both fluticasone propionate, an inhaled corticosteroid (ICS) and formoterol, a long acting beta$_2$ agonist (LABA); it is licensed for the regular treatment of asthma in adults where combination LABA and ICS therapy is appropriate. Both fluticasone and formoterol are well established in therapy and have strong efficacy and safety profiles.

PACEF reviewed a number of registration studies that demonstrate non-inferiority of *Flutiform* at various strengths to the equivalent dose components prescribed separately. Fluticasone/formoterol (*Flutiform*) MDI 50mcg/5mcg, 125/5 and 250/10 has also been demonstrated to be non-inferior to equivalent dose fluticasone/ salmeterol (*Seretide Evohaler*) MDI 50mcg/25mcg, 125/25 and 250/25. The close mirroring of the two formulations presents *Flutiform* as a potential lower cost alternative to *Seretide Evohaler*, particularly at the higher doses (see cost

comparison). However, it also means that both product ranges share similar flaws. The standard licensed dose of 2 puffs twice daily for each strength of *Flutiform* MDI and *Seretide Evohaler* means that, where a dosage change is required, a different strength of the same combination inhaler must be prescribed. By contrast, the licensed doses of the *Fostair* and *Symbicort* combination inhalers are more flexible (typically one or two puffs twice daily) allowing for step-up and step-down of doses without changing the inhaler.

A cost comparison reveals the following:

	Low strength	Medium strength	High strength
Flutiform MDI (fluticasone propionate/ formoterol)	50/5 micrograms 2 puffs twice daily **£18.00** (30 days treatment)	125/5 micrograms 2 puffs twice daily **£29.26** (30 days treatment)	250/10 micrograms 2 puffs twice daily **£45.56** (30 days treatment)
Fostair MDI (beclometasone dipropionate/ formoterol)	100/6 micrograms 1 puff twice daily **£14.66** (30 days treatment)	100/6 micrograms 2 puffs twice daily **£29.32** (30 days treatment)	Not available
Seretide Evohaler (fluticasone propionate/ salmeterol)	50/25 micrograms 2 puffs twice daily **£18.00** (30 days treatment)	125/25 micrograms 2 puffs twice daily **£35.00** (30 days treatment)	250/25 micrograms 2 puffs twice daily **£59.48** (30 days treatment)
Seretide Accuhaler (fluticasone propionate/ salmeterol)	100/50microgram 1 puff twice daily **£18.00** (30 days treatment)	250/50microgram 1 puff twice daily **£35.00** (30 days treatment)	500/50microgram 1 puff twice daily **£40.92** (30 days treatment)
Symbicort Turbohaler (budesonide/ formoterol)	200/6microgram 1 puff twice daily **£19.00** (30 days treatment)	200/6microgram 2 puffs twice daily **£38.00** (30 days treatment)	400/12microgram 2 puffs twice daily **£76.00** (2x60 dose units) (30 days treatment)

PACEF Recommendation:

***Flutiform* MDI is a new ICS/LABA combination inhaler containing two well established, well proven components, fluticasone propionate and formoterol. Trial evidence suggests non-inferiority to separate components and dose equivalent *Seretide Evohaler* formulations. Cost comparison reveals equivalent pricing to *Seretide Evohaler* at the lower strength (50/5microgram) and lower pricing to *Seretide Evohaler* at the higher strengths (125/5 and 250/10). There are theoretical savings from product switching from *Seretide Evohaler* at the higher strengths to equivalent dose *Flutiform*, although standard PACEF guidance is to review and step down high dose therapy where appropriate and the *Seretide Accuhaler* 500/50 represents a more cost-effective alternative to both products at the higher dose anyway. Despite these reservations, as both components are well established and the product is competitively priced, fluticasone/formoterol MDI (*Flutiform*) is designated GREEN.**

NICE TECHNOLOGY APPRAISAL 257: *LAPATINIB OR TRASTUZUMAB IN COMBINATION WITH AN AROMATASE INHIBITOR FOR THE FIRST-LINE TREATMENT OF METASTATIC HORMONE RECEPTOR-POSITIVE BREAST CANCER THAT OVEREXPRESSES HER2* (JUNE 2012)

Key Recommendations

- Lapatinib in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2).
- Trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone receptor-positive breast cancer that overexpresses HER2.
- Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor that is not recommended should have the option to continue treatment until they and their clinician consider it appropriate to stop.

PACEF Recommendation:
Lapatinib tablets 250mg (*Tyverb*) are designated RED-RED for this indication. Trastuzumab intravenous infusion (*Herceptin*) is designated RED-RED for this indication. Trastuzumab in combination with paclitaxel is recommended as an option for people with tumours expressing HER2 scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (see NICE Advanced breast cancer pathway). Designation: RED. Trastuzumab monotherapy is recommended as an option for people with tumours expressing HER2 scored at levels of 3+ who have received at least 2 chemotherapy regimens for metastatic breast cancer.

NICE TECHNOLOGY APPRAISAL 258: *ERLOTINIB FOR THE FIRST-LINE TREATMENT OF LOCALLY ADVANCED OR METASTATIC EGFR-TK MUTATION-POSITIVE NON SMALL CELL LUNG CANCER* (JUNE 2012)

Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if: (1) they test positive for the epidermal growth factor receptor tyrosine kinase (EGFRTK) mutation **and** (2) the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme.

PACEF Recommendation:
Erlotinib tablets (*Tarceva*) are designated RED for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC).

NICE TECHNOLOGY APPRAISAL 259: *ABIRATERONE FOR CASTRATION RESISTANT METASTATIC PROSTATE CANCER PREVIOUSLY TREATED WITH A DOCETAXEL-CONTAINING REGIMEN* (JUNE 2012)

Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if: (1) their disease has progressed on or after one docetaxel-containing chemotherapy regimen, and (2) the manufacturer provides abiraterone with the discount agreed in the patient access scheme.

PACEF Recommendation:
Abiraterone acetate 250mg tablets (*Zytiga*) are designated RED for the treatment of metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel containing chemotherapy regimen.

MHRA *DRUG SAFETY UPDATE*: SEPTEMBER TO NOVEMBER 2012

SEPTEMBER 2012

Oseltamivir (*Tamiflu*) - changed concentration and dosing dispenser of oral suspension from October 2012

From early October the strength of oseltamivir (*Tamiflu*) oral suspension has been changed to 6mg/ml. A new dosing dispenser calibrated in ml has been introduced concurrently. All prescriptions for *Tamiflu* this winter should state the dose in ml. The original 12mg/ml suspension is no longer available.

Dipeptidylpeptidase–4 inhibitors (DPP-4 inhibitors or gliptins) - risk of acute pancreatitis.

There have been some reports of acute pancreatitis associated with the use of DPP-4 inhibitors or gliptins. The incidence seems to be low ranging from 1/1000 to 1/100 patients, but precise figures are not known as few cases have been reported in clinical trials. In most cases symptoms have resolved following discontinuation of treatment. Patients taking DPP-4 inhibitors should be informed of the characteristic symptoms of acute pancreatitis – persistent severe abdominal pain (sometimes radiating to the back) - and encouraged to report any worrying signs to their GP or diabetic nurse specialist. If pancreatitis is suspected, the DPP- 4 inhibitor and any other medicines know to cause pancreatitis should be discontinued.

OCTOBER 2012

Agomelatine – risk of dose related hepatotoxicity and liver failure.

There have been several cases reports of serious hepatotoxicity with agomelatine including six reports of hepatic failure. Agomelatine is an antidepressant indicated for the treatment of major depressive disorders in adults.The risk of hepatic injury associated with agomelatine use was known at the time the product was first licensed in 2009 and prescribers have been advised to monitor regularly the liver function of patients prescribed this medication and to warn patients of the risk of hepatitis. A recent review of hepatotoxicity has shown that the frequency of elevated transaminases appears to be dose dependant and is higher in those on the 50mg dose than on the 25mg dose. In some cases hepatic reactions only occurred following an increase in dose.

The MHRA have issued the following advice to healthcare professionals

- Liver function tests (LFTs) should be undertaken in all patients receiving agomelatine at the initiation of treatment, at weeks 3,6,12 and 24 and periodically thereafter. LFTs should also be performed when increasing the dose of agomelatine (at the same time intervals as when initiating treatment) and whenever clinically indicated.

- Any patient with increased serum transaminases should have their LFTs repeated within 48 hours.
- Agomelatine should be immediately discontinued if an increase in serum transaminases exceeds 3 x the upper limit of normal or if patients present with symptoms or signs of potential liver injury (e.g. dark urine, pale stools, jaundice, pain in the right abdomen, sustained new onset and unexplained fatigue).
- Patients should be informed of the symptoms of potential liver injury and advised to stop taking agomelatine and seek urgent medical advice if symptoms occur.
- The benefits and risks of treatment should be discussed before initiating treatment in patients with existing elevated transaminase levels or risk factor(s) for hepatic injury (e.g. obesity, non alcoholic fatty liver disease, substantial alcohol intake, diabetes or use of concomitant medicines associated with risk of liver injury).
- Agomelatine is contraindicated in patients with hepatic impairment (i.e. cirrhosis or active liver disease).

PACEF Recommendations:
In June 2011, NICE appraised agomelatine (*Valdoxan*) and concluded that it could not be recommended for use on the NHS for the treatment of major depressive episodes. Nonetheless, local psychiatrists saw some value in the treatment and PACEF accepted a limited specialist role. As a result of this, agomelatine (*Valdoxan*) is designated RED for specialist use within LPFT only. Nonetheless, a recent review of primary care prescribing data has revealed that 225 items of agomelatine were prescribed over the last 6 months across 31 practices. All GPs currently prescribing agomelatine need to be aware of the safety concerns detailed above.

Denosumab - fatal cases of severe symptomatic hypocalcaemia and risk of hypocalcaemia

Denosumab 60mg injection (*Prolia*) is licensed for the treatment of osteoporosis in post menopausal women at increased risk of fractures and for the treatment of bone loss associated with hormonal ablation in men with prostate cancer. It is administered as a 60mg dose subcutaneously once every six months. Denosumab 120mg injection (*Xgeva*) is licensed for the prevention of skeletal events in adults with bone metastases from solid tumours and is administered once every 4 weeks. Hypocalcaemia is a known risk with denosumab especially in patients with severe renal impairment. Severe symptomatic hypocalcaemia resulting in three deaths has been reported in patients receiving denosumab 120mg; severe symptomatic hypocalcaemia has also been reported in patients at increased risk of hypocalcaemia receiving denosumab 60mg. Signs of hypocalcaemia include altered mental state, tetany, seizures and QTc prolongation. Hypocalcaemia normally occurs within 6 months of the first dose but can occur at any time during treatment.

The MHRA have issued the following advice to healthcare professionals

- Denosumab 120mg (for cancer indications) should not be used in patients with sever untreated hypocalcaemia.
- Denosumab 60mg (for osteoporosis indications) should not be used in patients with hypocalcaemia regardless of severity.
- Pre-existing hypocalcaemia must be corrected prior to initiating denosumab and supplementation of calcium and vitamin D is required in all patients receiving 120mg denosumab unless hypocalcaemia is present.

- Adequate intake of calcium and vitamin D is important in all patients receiving 60mg denosumab.
- Patients with severe renal impairment (creatinine clearance <30ml; eGFR 15-29ml/min/1.73m^2) or receiving dialysis are at greater risk of developing hypocalcaemia and monitoring of calcium levels in these patients is recommended.

PACEF comment
Denosumab 60mg injection (*Prolia*) is currently classified as RED on the Lincolnshire Traffic Lights List and is approved for secondary care use only. However, its status is currently under review in conjunction with the ULH rheumatology service. Denosumab 120mg injection (*Xgeva*) has not yet been approved for use and remains RED-RED at present.

Non-steroidal anti-inflammatory drugs (NSAIDs) - further evidence that the cardiovascular risk of diclofenac is higher than other non-selective NSAIDs and similar to the selective COX-2 inhibitors.

A new review of the cardiovascular safety of NSAIDs conducted by the European Medicines Agency (EMA) has highlighted further evidence that diclofenac is associated with cardiovascular risk factors that are higher than other non-selective NSAIDs and similar to the selective COX-2 inhibitors. Naproxen and low dose ibuprofen are still considered to have the most favourable cardiovascular safety profile of non-selective NSAIDS. The EMA are in the process of determining whether there is a need to update existing treatment advice for diclofenac.
In the interim healthcare professionals are reminded that when prescribing an NSAID the lowest effective dose should be used for the shortest time necessary to control symptoms. The patient's individual risk factors, including any history of cardiovascular and gastrointestinal illness should also be taken into account.

PACEF comment
Prescribing of diclofenac in Lincolnshire has reduced markedly since this issue was first identified as a priority two to three years ago. This safety reminder from the MHRA emphasizes the importance of ensuring that ibuprofen and naproxen remain the first and second line NSAIDs of choice in all practices and that creep back towards diclofenac is resisted wherever possible. Prescribers should remain alert to the increased CV risk associated with diclofenac, particularly at the higher doses.

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