Greater East Midlands Commissioning Support Unit

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

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 17 **October 2013**

What's new this month?

- **Linaclotide 290 microgram capsules (*Constella*) are approved for use for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. Designation: AMBER without shared care. In accordance with the product SPC, treatment should be reviewed after 4 weeks to determine whether there is sufficient evidence of benefit for therapy to continue (see page 3).**
- **Perampanel tablets (*Fycompa*) are approved for use as an option for the adjunctive treatment of partial-onset seizures with or without secondary generalisation, when standard adjunctive treatment has not provided an adequate response or has not been tolerated. Designation: AMBER without shared care (see page 4).**
- **Naloxone 2mg in 2ml intramuscular injection (*Prenoxad*) is approved for emergency use for complete or partial reversal of opioid-induced respiratory depression in the home, non-medical or health facility setting. It is designated GREEN although the bulk of initiations will be from secondary care. It is approved for inclusion in the *Joint Formulary* for this indication (see page 5).**
- ***Renavit* tablets are approved for the dietary management of water soluble vitamin deficiency in renal failure patients receiving dialysis. They can be prescribed in primary care at the request of Leicester Renal Services or following initiation from that service. Designation: AMBER without shared care (see page 5).**
- **Desogestrel 75 microgram tablet (*Cerazette*) is currently the most widely prescribed desogestrel containing progestogen only pill in Lincolnshire, but is approximately double the price of lower cost competitors. Prescribers are encouraged to review their prescribing of *Cerazette* with a view to moving patients to a lower cost brand. At present, desogestrel 75 microgram tablet (*Zelleta*) is the lowest cost product, although *Cerelle* and *Aizea* are also lower cost. All three products are designated GREEN and included on the *Joint Formulary*. Desogestrel 75 microgram tablets (*Cerazette*) are designated RED-RED. Due to the relatively high Category A *Drug Tariff* price, it is less costly to prescribe desogestrel 75 microgram tablets as a lower cost brand than as a generic (see page 6).**
- **There are now three ethinylestradiol 30 microgram /desogestrel 150 microgram combined oral contraceptive tablet formulations available in the UK: *Cimizt*, *Gedarel* 30/150 and *Marvelon*. Of these, *Cimizt* and *Gedarel 30/150* are lower cost and designated GREEN; both products are approved for inclusion in the *Joint Formulary*. In comparison, ethinylestradiol 30 microgram/desogestrel 150microgram tablets (*Marvelon*) are more expensive and should no longer be initiated in new patients; *Marvelon* is designated RED-RED and has been removed from the *Joint Formulary* (see page 7).**
- **Both latanoprost 50 microgram/ml (0.005%) preservative-free single dose eye drops (*Monoprost*) and bimatoprost 300 microgram per ml (0.03%) preservative-free single dose eye drops (*Lumigan*) are approved for use and are included in the *Joint Formulary*. Designation: AMBER without shared care. Tafluprost 15microgram/ml preservative-free single dose eye drops (*Saflutan*) have been removed from the *Formulary* and re-designated RED-RED (see page 7).**

- **There is now high quality evidence that shows tamoxifen to be effective in reducing breast cancer incidence when used for chemoprevention in pre and post-menopausal women who do not have a diagnosis of breast cancer. As a result of this the new NICE Clinical Guideline on familial breast cancer has recommended that tamoxifen 20mg daily for 5 years should be offered to women at high risk of breast cancer and considered for those at moderate risk. Raloxifene (*Evista*) 60mg daily has similar effectiveness to tamoxifen in post-menopausal women who do not have a diagnosis of breast cancer. NICE have recommended that raloxifene should be offered to post-menopausal women at high risk and considered for those at moderate risk. Where both drugs are indicated, generic tamoxifen 20mg is preferred on cost grounds. Neither of these drugs currently holds a marketing authorisation for these indications. Both drugs are designated GREEN within this context (see page 8).**

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SUMMARY OF PACEF DECISIONS: *SEPTEMBER 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Bimatoprost 300microgram/ml preservative-free single dose eye drops (*Lumigan*)	For use as monotherapy or as an adjunct to beta-blockers in chronic open-angle glaucoma or ocular hypertension	AMBER without shared care Approved for inclusion in the *Joint Formulary*
Desogestrel 75 microgram tablet (*Aizea*)	Oral contraception	GREEN Approved for inclusion in the *Joint Formulary*
Desogestrel 75 microgram tablet (*Cerazette*)	Oral contraception	RED-RED Removed from the *Joint Formulary*. Should no longer be initiated in new patients.
Desogestrel 75 microgram tablet (*Cerelle*)	Oral contraception	GREEN Approved for inclusion in the *Joint Formulary*
Desogestrel 75 microgram tablet (*Zelleta*)	Oral contraception	GREEN Approved for inclusion in the *Joint Formulary*
Ethinylestradiol 30 microgram/desogestrel 150 microgram tablets (*Cimizt*)	Oral contraception	GREEN Approved for inclusion in the *Joint Formulary*
Ethinylestradiol 30 microgram/desogestrel 150 microgram tablets (*Gedarel*)	Oral contraception	GREEN Approved for inclusion in the *Joint Formulary*
Ethinylestradiol 30 microgram/desogestrel 150 microgram tablets (*Marvelon*)	Oral contraception	RED-RED Removed from the *Joint Formulary*. Should no longer be initiated in new patients.
Latanoprost 50microgram/ml preservative-free single dose eye drops (*Monoprost*)	Open angle glaucoma, ocular hypertension	AMBER without shared care Approved for inclusion in the *Joint Formulary*
Linaclotide 290 microgram capsules (*Constella*)	For the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C)	AMBER without shared care Approved for inclusion in the *Joint Formulary*

	in adults	
Naloxone 2mg in 2ml intramuscular injection (Prenoxad)	For emergency use for complete or partial reversal of opioid-induced respiratory depression in the home, non-medical or health facility setting.	GREEN although the majority of initiations will be from secondary care. Approved for inclusion in the *Joint Formulary*
Perampanel 2mg/ 4mg/ 6mg/ 8mg/10mg/ 12mg tablets (*Fycompa*)	For use as an adjunct in partial-onset seizures with or without secondary generalisation	AMBER without shared care. Approved for inclusion in the *Joint Formulary*.
Raloxifene 60mg tablets (*Evista*)	For chemoprevention in post-menopausal women at moderate to high risk of breast cancer who do not have a diagnosis of breast cancer. Raloxifene does not have a marketing authorisation for this indication.	GREEN Second line alternative to tamoxifen 20mg tablets
Renavit water soluble vitamin tablets	For the dietary management of water soluble vitamin deficiency in renal failure patients receiving dialysis	AMBER without shared care. Approved for inclusion in the *Joint Formulary*.
Tafluprost 15microgram/ml preservative-free single dose eye drops (*Saflutan*)	For raised intra-ocular pressure in open-angle glaucoma or ocular hypertension.	RED-RED Removed from the *Joint Formulary*
Tamoxifen 20mg tablets	For chemoprevention in pre and post-menopausal women at moderate to high risk of breast cancer who do not have a diagnosis of breast cancer. Tamoxifen does not have a marketing authorisation for this indication.	GREEN First line

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS in Lincolnshire website (www.lincolnshire.nhs.uk); follow the commissioning link to PACEF. Electronic copies of both the *PACE Bulletin* and our sister publication *PACE Shorts* (a short summary of the *PACE Bulletin*) are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk

NEW DRUG ASSESSMENT: *LINACLOTIDE 290 MICROGRAM CAPSULES (CONSTELLA)*

Linaclotide (*Constella*) is the first of a new class of drugs known as the guanylate cyclase – C receptor agonists; it is authorized for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

PACEF evaluated two randomised double blind placebo controlled trials. In the first of these 800 patients aged 18 to 84 with a mean Body Mass Index of 28 and IBS-C were randomized to either 290 microgram of linaclotide daily or placebo for 12 weeks. Linaclotide performed better than placebo in terms of both percentage of patients demonstrating improvement in abdominal symptoms (54.8% vs 41.8% for placebo) and percentage of patients demonstrating IBS symptom relief (37% vs 18.5% for placebo). The second trial ran for 26 weeks and augmented the findings of the first. Both revealed that diarrhoea was the most common adverse reaction occurring in almost 20% of patients; in about a quarter of these, diarrhoea was severe enough to warrant withdrawal from the trial. Neither of these trials provide long-term safety or efficacy data, nor do they enable comparison with any alternative therapy. Both trials allowed concomitant use of bisacodyl; the 12 week trial allowed ongoing use of fibre, bulk laxatives, stool softeners and probiotics.

A cost comparison reveals that linaclotide is significantly more expensive than alternative therapies:

Drug	Daily dose range	Cost (£)pa
Linaclotide 290 microgram capsules (*Constella*)	One capsule daily	£488
Laxatives		
Bisacodyl 5mg tablets	5-20mg daily	£12.48- £49.94
Ispaghula husk granules	1 sachet three times daily	£85.80
Antispasmodics		
Peppermint oil 0.2ml capsules	1-2 caps three times daily	£91.52-£183.04
Hyoscine butylbromide 10mg tablets	10mg three times daily to 20mg four times daily	£58.50 - £156
Mebeverine hydrochloride 135mg tablets	135mg three times daily	£51.76
Antidepressants		
Amitriptyline tablets	10-30mg once daily	£11.7 - £35.10
Fluoxetine 20mg capsules	20mg daily	£12.84

The Summary of Product Characteristics (SPC) for linaclotide advises that patients should be reviewed after 4 weeks of therapy and that treatment may need to be discontinued if the patient shows insufficient evidence of benefit. NICE Clinical Guideline 61 on the management of IBS recommends that first-line treatment should be advice on lifestyle and diet. If pharmacological treatment is required the choice should be based on the predominant symptom. In terms of IBS with constipation this would be laxatives and antispasmodic agents; unlicensed use of either a tricyclic antidepressant or a selective serotonin reuptake inhibitor (SSRI) may be considered if laxatives and antispasmodics prove ineffective.

PACEF Recommendation

From the limited short-term trial evidence available, linaclotide (*Constella*) emerges as superior to placebo with up to 55% of patients showing some relief of abdominal symptoms and 37% relief of IBS symptoms. However, the placebo response in these trials is high and the cost of therapy significantly higher than alternative therapies; this raises concerns about the overall cost-effectiveness of the product. With this in mind, linaclotide 290 microgram capsules (*Constella*) are designated AMBER without shared care. Linaclotide should be reserved for patients with IBS-C in whom other treatment options are inappropriate or ineffective. It should only be initiated by a gastroenterologist and, in accordance with the product SPC, treatment should be reviewed after 4 weeks to determine whether there is sufficient evidence of benefit for therapy to continue. Linaclotide 290 microgram capsules (*Constella*) are approved for inclusion in the *Joint Formulary* for this indication.

NEW DRUG ASSESSMENT: *PERAMPANEL TABLETS (FYCOMPA)*

Perampanel (*Fycompa*) is a new first in class selective non-competitive antagonist of the AMPA glutamate receptor. It is authorized for use as an adjunctive treatment for partial-onset seizures with or without secondary generalised seizures in people aged 12 years and older with epilepsy.

Supporting evidence comes from three phase III randomised, double-blind, placebo-controlled trials in patients aged ≥12 years with a diagnosis of epilepsy with partial seizures, with or without secondary generalisation. These trials demonstrated that adjunctive treatment with perampanel 4 to 12 mg once daily achieved a statistically significant reduction in seizure frequency compared to placebo. The very low number of patients aged 64 years or over recruited into the trials means that uncertainty remains as to whether these results can be reliably extrapolated to an elderly population.

As perampanel is authorized for use in adolescent patients aged ≥12 years, it has an advantage over alternative recently licensed anti-epileptic drugs (AEDs) such as lacosamide

(*Vimpat*) (approved for use in adults aged ≥16 years), eslicarbazepine (*Zebinix*) and retigabine (*Trobalt*) (approved for use in adults ≥18 years).

There was a high incidence of dizziness reported in trials; elderly patients may be more susceptible with increased risk of falling identified as a potential safety concern. There is no data available to inform a comparison between perampanel and other AEDs. A cost comparison reveals perampanel to be one of the more expensive agents, although flat pricing across the different strengths means that it is competitively priced at the higher doses.

PACEF Recommendation:
Perampanel tablets (*Fycompa*) are approved for use as an option for the adjunctive treatment of partial-onset seizures with or without secondary generalisation, when standard adjunctive treatment (with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate) has not provided an adequate response, or has not been tolerated. Designation: AMBER without shared care. Treatment should only be initiated by a physician with appropriate experience in the treatment of epilepsy; LPFT envisage that a small number of patients each year will be initiated on perampanel through their specialist epilepsy clinic. Perampanel tablets (*Fycompa*) are approved for inclusion in the *Joint Formulary* for this indication.

NEW DRUG ASSESSMENT: *NALOXONE 2MG IN 2ML INJECTION (PRENOXAD)*

*Prenoxad i*s an intra-muscular injectable form of naloxone authorized for emergency use for complete or partial reversal of opioid-induced respiratory depression in the home, non-medical or health facility setting. It offers a new use for naloxone in so called 'take-home' programmes designed to reduce harm when used as part of a resuscitation intervention in suspected opioid overdose that occurs in a domestic setting. *Prenoxad* injection is administered intramuscularly as part of resuscitation in suspected overdose casualties where opioid drugs may be involved. It can be administered every 2 to 3 minutes between resuscitation cycles and continued until ambulance services arrive or the person regains consciousness. Non-healthcare professionals such as partners, carers or family members can be trained to administer the drug intramuscularly in such an emergency. All clients taking either elicit opiate-related drugs or prescribed opiate related drugs such as methadone could potentially benefit from the availability of *Prenoxad* injection. Naloxone is already well established as an effective treatment for the complete or partial reversal of opioid-induced respiratory depression.

PACEF Recommendation:
Naloxone 2mg in 2ml intramuscular injection (*Prenoxad*) is approved for emergency use for complete or partial reversal of opioid-induced respiratory depression in the home, non-medical or health facility setting. It is designated GREEN although the bulk of initiations should only be from clinicians working within drug rehabilitation or substance misuse services. It is approved for inclusion in the *Joint Formulary* for this indication

RAPID DRUG ASSESSMENT: *RENAVIT WATER SOLUBLE VITAMIN TABLETS*

Renavit water soluble vitamin tablets have recently been launched for the treatment of water soluble vitamin deficiency in patients with renal failure on dialysis. *Renavit* is not a licensed pharmaceutical, but is classed as a nutritional supplement and approved for prescribing on the NHS as a borderline substance. The product provides approximately the recommended

daily amounts of the water soluble vitamins (B1, B2, B3, B5, B6, B8, B9, B12 and C) but, crucially, and unlike other multivitamin preparations, does not contain vitamins A, D or E. Vitamins A, D and E have the potential to cause toxicity in renal dialysis patients as they are not removed during the dialysis process.

In 2010, the UK Renal Association issued a clinical practice guideline entitled *Nutrition in Chronic Kidney Disease* that recommended that water soluble vitamins should be prescribed for haemodialysis patients. Renal Services at Leicester General Hospital have previously used *Dialyvite* tablets for this indication, a food supplement that delivers the same range and strength of vitamins as *Renavit,* but at a slightly higher cost.

PACEF Recommendation:
***Renavit* water soluble vitamin tablets are designated AMBER without shared care for the treatment of water soluble vitamin deficiency in patients with renal failure on dialysis. They can be prescribed in primary care at the request of Leicester Renal Services or following initiation from that service. *Renavit* tablets are approved for inclusion in the *Joint Formulary*.**

RAPID DRUG ASSESSMENTS: *DESOGESTREL 75 MICROGRAM TABLETS (AIZEA/ CERAZETTE/CERELLE/ZELLETA)*

Desogestrel 75 microgram tablet (*Aizea*) is a new lower cost progestogen only oral contraceptive pill (POP). It is directly equivalent to a number of other desogestrel containing POPs already on the UK market:

Product	Pack size	Cost (£)
Desogestrel 75 microgram tablet (*Aizea*)	3 x 28 tabs	£5.21
Desogestrel 75 microgram tablet (*Cerazette*)	3 x 28 tabs	£8.68
Desogestrel 75 microgram tablet (*Cerelle*)	3 x 28 tabs	£4.30
Desogestrel 75 microgram tablet (*Zelleta*)	3 x 28 tabs	£3.51
Desogestrel (Cat A Drug Tariff price)	3 x 28 tabs	£7.12

PACEF Recommendation:
Desogestrel 75 microgram tablet (*Cerazette*) is currently the most widely prescribed desogestrel containing POP in Lincolnshire but is approximately double the price of lower cost competitors. Prescribers are encouraged to review their prescribing of *Cerazette* with a view to moving patients to a lower cost brand. At present, desogestrel 75 microgram tablet (*Zelleta*) is the lowest cost product, although *Cerelle* and *Aizea* are also lower cost. All three products are designated GREEN and included on the *Joint Formulary*. Desogestrel 75 microgram tablets (*Cerazette*) are designated RED-RED. Due to the relatively high Category A *Drug Tariff* price, it is less costly to prescribe desogestrel 75 microgram tablets as a lower cost brand than as a generic. The table below estimates the annual saving within each of the Lincolnshire CCGs if all desogestrel 75 microgram tablets were prescribed as the lowest cost brand *Zelleta*.

Clinical Commissioning Group	Potential Annual Saving if all desogestrel 75 microgram tablets prescribed as the lowest cost brand
Lincolnshire East CCG	£57,126
Lincolnshire West CCG	£62,359
South Lincolnshire CCG	£42,089
South West Lincolnshire CCG	£32,302

RAPID DRUG ASSESSMENT: ETHINYLESTRADIOL 30 MICROGRAM/ DESOGESTREL 150 MICROGRAM TABLETS (*CIMIZT*)

Ethinylestradiol 30mcg/desogestrel 150mcg tablet (*Cimizt*) is a newly launched lower cost combined oral contraceptive (COC). It is an identical combination to two directly equivalent products that are already in use across the county: *Gedarel* 30/150 and *Marvelon.* A cost comparison reveals the following:

Product	Pack size	Cost (£)
Ethinylestradiol 30mcg/desogestrel 150mcg tablet (*Cimizt*)	3 x 21 tabs	£4.53
Ethinylestradiol 30mcg/desogestrel 150mcg tablet (*Gedarel 30/150*)	3 x 28 tabs	£4.93
Ethinylestradiol 30mcg/desogestrel 150mcg tablet (*Marvelon*)	3 x 21 tabs	£6.45

PACEF Recommendation:

There are now three ethinylestradiol 30 microgram /desogestrel 150 microgram combined oral contraceptive tablet formulations available in the UK: *Cimizt*, *Gedarel* 30/150 and *Marvelon*. Of these, *Cimizt* and *Gedarel 30/150* are lower cost and designated GREEN; both products are approved for inclusion in the *Joint Formulary*. In comparison, ethinylestradiol 30 microgram/desogestrel 150microgram tablets (*Marvelon*) are more expensive and should no longer be initiated in new patients; *Marvelon* is designated RED-RED and has been removed from the *Joint Formulary*.

UPDATED RAPID DRUG ASSESSMENT: LATANOPROST 50 MICROGRAM/ML (0.005%) (*MONOPROST*) AND BIMATOPROST 300 MICROGRAM/ML (0.03%) (*LUMIGAN*) PRESERVATIVE FREE SINGLE DOSE EYE DROPS

[This is an updated version of a Rapid Drug Assessment that originally appeared in *PACE Bulletin* Vol 7 Number 14 (August 2013)].

Latanoprost 50 microgram/ml (0.005%) preservative-free single dose eye drops (*Monoprost*) and bimatoprost 300 microgram per ml (0.03%) preservative-free single dose eye drops (*Lumigan*) are newly launched prostaglandin analogue eye preparations licensed for use in open angle glaucoma and ocular hypertension. Both products are already approved for use as multi-dose preservative containing formulations and appear on the *Joint Formulary*. Previously, the tafluprost 15 microgram/ml preservative free single dose formulation (*Saflutan*) was the only preservative-free product available. A cost comparison reveals that both the latanoprost and bimatoprost formulations are lower in cost than the tafluprost formulation with the latanoprost product being the lowest cost option:

Product	Pack Size	Cost
Bimatoprost 300microgram/ml preservative-free single dose eye drops (*Lumigan*)	30 x 0.4ml	£13.75
Latanoprost 50microgram/ml preservative-free single dose eye drops (*Monoprost*)	30 x 0.2ml	£8.49
Tafluprost 15microgram/ml preservative-free single dose eye drops (*Saflutan*)	30 x 0.3ml	£17.41

PACEF Recommendation:

Both latanoprost 50 microgram/ml (0.005%) preservative-free single dose eye drops (*Monoprost*) and bimatoprost 300 microgram per ml (0.03%) preservative-free single

dose eye drops (*Lumigan*) are approved for use and are now included in the *Joint Formulary*. Designation: AMBER without shared care. Tafluprost 15 microgram/ml preservative-free single dose eye drops (*Saflutan*) are significantly higher in cost that these alternatives and have been re-classified from AMBER to RED-RED; this product has also been removed from the *Joint Formulary*.

NICE UPDATE

NICE CLINICAL GUIDELINE 164: *FAMILIAL BREAST CANCER* (JUNE 2013)

NICE recently published Clinical Guideline 164: *Familial breast cancer – Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer* (June 2013). The key recommendations are as follows:

- When a person with no personal history of breast cancer presents with breast symptoms or has concerns about relatives with breast cancer, a first- and second-degree family history should be taken in primary care to assess risk, because this allows appropriate classification and care.
- First degree relatives are defined as: mother, father, daughter, son, sister or brother.
- Second degree relatives are: grandparent, grandchild, aunt, uncle, niece, nephew, half-sister or half-brother
- Healthcare professionals should respond to a person who presents with concerns but should not, in most instances, actively seek to identify people with a family history of breast cancer.
- People without a personal history of breast cancer who meet the following criteria should be offered referral to secondary care:
    a. one first-degree female relative diagnosed with breast cancer at younger than age 40 years **or**
    b. one first-degree male relative diagnosed with breast cancer at any age **or**
    c. one first-degree relative with bilateral breast cancer where the first primary was diagnosed at younger than age 50 years **or**
    d. two first-degree relatives, or one first-degree **and** one second-degree relative, diagnosed with breast cancer at any age **or**
    e. one first-degree or second-degree relative diagnosed with breast cancer at any age **and** one first-degree or second-degree relative diagnosed with ovarian cancer at any age (one of these should be a first-degree relative) **or**
    f. three first-degree or second-degree relatives diagnosed with breast cancer at any age.
- Women aged over 35 years with a family history of breast cancer should be informed of an increased risk of breast cancer associated with taking the oral contraceptive pill, given that their absolute risk increases with age.
- Women should be advised to breastfeed if possible because this is likely to reduce their risk of breast cancer, and is in accordance with general health advice.
- Women with a family history of breast cancer who are considering taking, or already taking, hormone replacement therapy (HRT) should be informed of the increase in breast cancer risk with type and duration. HRT usage in a woman at familial risk should be restricted to as short a duration and as low a dose as possible. Oestrogen-only HRT should be prescribed where possible.
- A woman having an early (natural or artificial) menopause should be informed of the risks and benefits of HRT, but generally HRT usage should be confined to women younger than age 50 years if at moderate or high risk.
- Alternatives to HRT should be considered for specific symptoms such as osteoporosis or menopausal symptoms.

- Women with a family history of breast cancer should be informed that alcohol may increase their risk of breast cancer slightly.
- Women should be advised not to smoke, in line with current health advice.
- Women should be advised on the probable increased postmenopausal risk of breast cancer from being overweight.
- Women should be advised about the potential benefits of physical exercise on breast cancer risk.

Chemoprevention for women with no personal history of breast cancer

- Healthcare professionals within a specialist genetic clinic should discuss and give written information on the absolute risks and benefits of all options for chemoprevention to women at high risk or moderate risk of breast cancer (defined in the table below). Discussion and information should include the side effects of drugs, the extent of risk reduction, and the risks and benefits of alternative approaches, such as risk-reducing surgery and surveillance.

Breast cancer risk category			
	Near population risk	**Moderate risk**	**High risk** [1]
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3–8%	Greater than 8%

[1]This group includes known *BRCA1*, *BRCA2* and *TP53* mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (*STK11*), Cowden (*PTEN*) and familial diffuse gastric cancer (E-Cadherin).

For women at 'high risk'

- Offer tamoxifen for 5 years to premenopausal women at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer.

PACEF Comment: *Tamoxifen*
Tamoxifen can increase the risk of thromboembolism particularly during and immediately after major surgery or periods of immobility. Tamoxifen causes endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma. Patients should be informed of the risk of endometrial cancer and told to report relevant symptoms promptly.

- Offer tamoxifen for 5 years to postmenopausal women without a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or they have a past history of endometrial cancer.
- Offer either tamoxifen or raloxifene for 5 years to postmenopausal women with a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of *thromboembolic* disease or endometrial cancer.

PACEF Comment: *Raloxifene*
Raloxifene should be used with caution where there are risk factors for venous thromboembolism, Raloxifene is contra-indicated in patients with a history of venous

thromboembolism or endometrial cancer. Raloxifene may reduce the incidence of oestrogen-receptor positive breast cancer but its role in established breast cancer is not yet clear.

- Do not offer tamoxifen or raloxifene to women who were at high risk of breast cancer but have had a bilateral mastectomy.

For women at 'moderate risk'

- Consider prescribing tamoxifen for 5 years to premenopausal women at moderate risk of developing breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer.
- Consider prescribing tamoxifen for 5 years to postmenopausal women without a uterus and at moderate risk of developing breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or they have a past history of endometrial cancer.
- Consider prescribing either tamoxifen or raloxifene for 5 years to postmenopausal women with a uterus and at moderate risk of developing breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer.
- Do not continue treatment with tamoxifen or raloxifene beyond 5 years.
- Inform women that they should stop tamoxifen at least 2 months before trying to conceive or 6 weeks before elective surgery.

Evidence base

Since the publication of the previous NICE Clinical Guideline on *Familial Breast Cancer* (2006) two trials have been published on chemoprevention. These have provided high quality evidence that shows **tamoxifen to be effective in reducing breast cancer incidence when used for chemoprevention in pre and post-menopausal women who do not have a diagnosis of breast cancer.** These trials are:

- Fisher et al 2005, Tamoxifen for the prevention of breast cancer, *Journal of the National Cancer Institute*
- Cuzick et al 2007, Long term results of tamoxifen prophylaxis for breast cancer – 96 month follow-up of the randomized International Breast Cancer Intervention Study, *Journal of the National Cancer Institute*

There is also high quality evidence which suggests that **raloxifene has similar effectiveness to tamoxifen when used for chemoprevention in post- menopausal women who do not have a diagnosis of breast cancer:**

- Vogel et al 2006, Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes, *JAMA*

The doses used in these trials were tamoxifen 20mg daily for 5 years and raloxifene 60mg daily for 5 years:

	Dose	5 years therapy
Tamoxifen 20mg tablets	20mg daily	£146.61
Raloxifene 60mg tablets (*Evista*)	60mg daily	£1,111.95

Drug Tariff, October 2013

PACEF Comment:
Generic tamoxifen 20mg tablets are significantly lower in cost than raloxifene 60mg tablets (*Evista*) at present and should be preferred where indicated. Raloxifene should only be used in postmenopausal women where tamoxifen is poorly tolerated or considered inappropriate. At the time of publication, neither tamoxifen nor raloxifene have UK marketing authorisations for the prevention of breast cancer.

Acknowledgements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, GEM CSU, Robyn Thompson, Senior Pharmacist, ULH and Shiraz Haider, Chief Pharmacist, LPFT for their help in the compilation of this *Bulletin*.

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October 2013