NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 5; Number 8 **May 2011**

What's new this month:

- **Dovobet Gel is approved for use in scalp and non-scalp plaque psoriasis (see page 3).**
- **A new quinolone eye drop for bacterial conjunctivitis, moxifloxacin (Moxivig), is not approved for use (see page 4).**
- **Nicorette Fresh Mint Lozenges are approved for use as part of the wider range of nicotine replacement therapy available to support smoking cessation (see page 5)**
- **GPs are urged to stop prescribing Diconal due to the high risk of misuse and diversion (see page 6).**
- **Advice is given on the donation of patient-returned medicines to charitable organisations supporting medical care in the developing world (see page 7).**
- **Pharmaceutical waste is reviewed in a national report (see page 8).**
- **Limited support to help practices reduce high prescribing volume is offered to Consortia (see page 9).**
- **The NICE Clinical Guidelines on the management of heart failure is reviewed (see page 11).**

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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: MARCH 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Bendamustine injection (Levact)	Licensed for the treatment of chronic lymphocytic leukaemia	RED
Bevacizumab intravenous infusion (Avastin)	Licensed for the treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy Licensed for the first line treatment of metastatic breast cancer in combination with paclitaxel or docetaxel	RED-RED RED-RED
Calcipotriol 50 microgram/g and betamethasone 500 microgram/g gel (Dovobet Gel)	Licensed for scalp psoriasis and for mild to moderate non-scalp plaque psoriasis.	GREEN
Dipipanone 10mg/cyclizine 30mg tablets (Diconal)	Licensed for moderate to severe pain	RED-RED NHSL Accountable Officer for Controlled Drugs and Lincolnshire Police have requested that all prescribing should cease to mitigate the risk of drug misuse and diversion.
Modafinil tablets (Provigil)	Licensed for the treatment of daytime sleepiness associated with narcolepsy Licensed for the treatment of daytime sleepiness associated with obstructive sleep apnoea syndrome Licensed for the treatment of daytime sleepiness associated with chronic shift work	AMBER RED-RED RED-RED
Moxifloxacin hydrochloride 0.5% eye drops (Moxivig)	Licensed for the topical treatment of purulent bacterial conjunctivitis.	RED-RED
Nicorette Fresh Mint Lozenges	Licensed for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years. It is also indicated for use in pregnant and lactating women.	GREEN
Pazopanib tablets (Votrient)	Licensed for the first-line treatment of advanced renal cell carcinoma.	RED
Perindopril arginine (Coversyl Arginine)	Licensed for hypertension, symptomatic heart failure and prophylaxis of cardiac events following MI or revascularisation in stable coronary artery disease	RED-RED

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.**

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

RAPID DRUG ASSESSMENT: CALCIPOTRIOL AND BETAMETASONE GEL (DOVOBET)

Dovobet Gel (Calcipotriol 50 microgram/g and betamethasone 500 microgram/g) is a once daily vitamin D analogue/ corticosteroid gel formulation licensed both for scalp psoriasis and for mild to moderate non-scalp plaque psoriasis. The scalp and non-scalp license allows for a single product to be used on different areas of the body and scalp. This potentially reduces the need for multiple products to be in use at the same time in the same patient. In addition, some patients find gel formulations to be more cosmetically acceptable than ointments. The recommended treatment period is 4 weeks for scalp areas and 8 weeks for non-scalp areas.

PACEF considered three trials:

- In a multi-centre, prospective, double-blind study of 364 patients with at least mild psoriasis vulgaris on the trunk and or limbs, patients were randomized to receive once daily treatment with Dovobet gel or betametasone dipropionate 0.5mg/g gel or calcipotriol 50mg/g or the gel vehicle. The primary objective was to compare the efficacy and safety of the treatments. At weeks 4 and 8, the percentage of responders according to an investigators global assessment (IGA) scale was higher in the Dovobet gel arm than in any of the other arms and the mean percentage change in psoriasis area and severity index (PASI) was greater in the Dovobet gel arm compared to the other treatments (although not always statistically significant). The investigators also commented that, although Dovobet gel and ointment have not been tested head-to-head, the data suggest that the ointment is likely to be more efficacious than the gel probably due to the occlusive effect of the ointment.
- In a 52 week double blind study with 869 patients with moderate to severe scalp psoriasis, patients were randomized to receive betametasone dipropionate 0.5mg/g and calcipotriol 50 micrograms/g (Dovobet gel) or calcipotriol 50 micrograms/g alone. Primary response criteria were the incidences of both adverse drug reactions of any type and of adverse events of concern associated with long term corticosteroid use on the scalp. Secondary criteria included efficacy of treatment based on global assessment of disease severity and patient ratings of the treatments efficacy. According to the IGA of disease severity, the number of patients who reached satisfactorily controlled disease was higher in the Dovobet gel arm vs. the calcipotriol arm.
- In an 8-week multicentre prospective randomized double blind placebo controlled trial in patients with scalp psoriasis, patients were randomized to either Dovobet gel, each constituent separately or the gel vehicle. The primary efficacy measure was the percentage of patients reaching absence of disease or very mild disease according to the IGA at 8 weeks. Investigators also assessed disease in terms of the three clinical signs of redness, thickness and scaliness; patients assessed their own disease in relation to improvement from baseline on a 7 point scale. The results showed Dovobet Gel to be significantly more effective than the other treatments from week 2 onwards. By week 4, the proportion of patients experiencing absent or mild disease was as follows: Dovobet Gel 66.9%, betametasone dipropionate 54.7%, calcipotriol 23.5% and gel vehicle 14.7%.

A cost comparison reveals the following:

Drug	Dose	Cost/pack
Dovobet Gel	Once a day for 4-8 weeks	£36.50 for 60g
Xamiol Gel	Once a day for 4 weeks	£36.50 for 60g
Dovobet ointment	Once a day for 4 weeks	£32.99 for 60g
Coal Tar Scalp Ointment	Daily for 3-7 days then once a week	£4.54 for 40g
Trimovate	Once to twice a day	£6.70 for 60g

PACEF Recommendation:
PACEF are convinced from trial evidence that Dovobet gel is more effective than its single constituents prescribed alone. The wider range of licensed indications (both scalp and non-scalp psoriasis) make it a preferable alternative to Xamiol gel (contains the same components in the same quantities but licensed for scalp psoriasis only). The scalp and non-scalp psoriasis license and the once daily dosage frequency also allow some scope for simplification of multi-component treatment regimes. While the ointment formulation of Dovobet is potentially more efficacious, the gel formulation may be preferred cosmetically by some patients. As a result of this, Dovobet gel is designated GREEN. As Dovobet gel and Xamiol gel contain the same components, but are licensed differently, it is recommended that both products are prescribed by brand.

RAPID DRUG ASSESSMENT: MOXIFLOXACIN HYDROCHLORIDE 0.5% EYE DROPS (MOXIVIG)

Moxifloxacin hydrochloride 0.5% eye drops (Moxivig) are licensed for the topical treatment of purulent bacterial conjunctivitis. Moxifloxacin is a new fourth generation fluoroquinolone antibiotic. Despite several requests, no trial data supporting the use of moxifloxacin eye drops was provided by the manufacturer; a literature search identified no systematic reviews or meta-analyses relating to the use of moxifloxacin within this context.

A cost comparison reveals the following:

Drug	Daily dose range	Cost (£) per 5ml bottle
Moxifloxacin 0.5% eye drops (Moxivig)	1 drop 3 times daily	£9.80
Ciprofloxacin 0.3% eye drops (Ciloxan)	1 or 2 drops four times daily	£4.70
Levofloxacin 5mg/ml eye drops (Oftaquix)	1 or 2 drops every 2 hours up to 8 times daily when awake for the first 2 days then 1 or 2 four times daily	£6.95
Ofloxacin 0.3% eye drops (Exocin)	1 or 2 drops every 2 to 4 hours on the first 2 days then 1 or 2 drops four times daily	£2.17

PACEF Recommendation:
Lincolnshire *Guidelines for the treatment of commonly occurring infections in primary care* (Winter 2010/11) recommend that, for most people with bacterial conjunctivitis, topical antibiotics make little or no difference to recovery. Delayed or post-dated prescriptions should be considered as an option. Prescribing an antibiotic should be considered if infective conjunctivitis is severe. Cases of severe contact lens conjunctivitis should be referred to an ophthalmologist to eliminate risk of acanthamoeba. Where treatment is indicated, chloramphenicol 0.5% eye drops 2 hourly for 2 days then 4 hourly (whilst awake) plus chloramphenicol eye ointment 1% at night should be considered first line. Fusidic acid 1% gel twice daily offers an appropriate second line alternative. Treatment should continue for 48 hours beyond the resolution of symptoms. The role of quinolone eye drops within this context is extremely limited. Local microbiologists have advised severe restriction on the use of quinolones in any context due to major concerns over increasing microbial resistance. In addition, moxifloxacin eye drops are expensive in comparison to alternative quinolones and lower cost first and second line alternatives. Designation: RED-RED.

RAPID DRUG ASSESSMENT: NICORETTE FRESH MINT LOZENGES

Nicorette Fresh Mint Lozenges are a recently launched addition to the already well established Nicorette range. The product is licensed for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years. It is also indicated for use in pregnant and lactating women.

A cost comparison reveals that the product is comparably priced to other forms of nicotine replacement therapy (NRT) both in the Nicorette range and in other NRT formulations.

Drug	Daily dose range	Cost (£) & number of patches
Nicorette fresh mint lozenge 2mg	8-12 lozenges per day	£2.55 (24) £8.29 (96)
Alternative oral products – Nicorette range		
Nicorette micro tabs 2mg (lemon flavour)	1-2 when required maximum dose 40 tabs	£3.99 (30) £11.12 (105)
Nicorette gum 2mg	Maximum 15 daily	£3.25 (30) £8.89 (105)
Nicorette gum 4mg	Maximum 15 daily	£3.99 (30) £10.83 (105)
Alternative Nicorette products		
Nicorette Invisipatch 10mg/15mg/25mg	One patch daily- 12 week course	£9.97 (7) 12 week course £119.64
Nicorette transdermal 5mg/10mg/15mg	One patch daily 13 week course	£9.07 (7) 12 week course £108.84
Nicorette nasal spray	1 spray each nostril twice an hour to max of 64 sprays per day for 8 weeks then reduce over 4 weeks	£13.40 per 200 sprays. At max dose 1 spray lasts just over 3 days.
Nicorette inhalator	Inhale when required. Max 12 cartridges a day. Reduce use over time	£4.46 (6) £14.01 (42 cartridges)

Alternative oral products		
NiQuitin lozenges 2mg	Max 15 daily	£5.12 (36) £9.97 (72)
NiQuitin lozenges 4mg	Max 15 daily	£5.12 (36) £8.93 (60) £9.97 (72)
NiQuitin gum 2mg	Max 15 daily	£1.71 (12) £3.25 (24) £9.97 (96)
NiQuitin gum 4mg	Max 15 daily	
Nicotinell 4mg gum	Max 15 daily	£10.26 (96)
Nicotinell 1mg lozenge	Max 30 daily	£9.12 (96)
Nicotinell 2mg lozenge	Max 15 daily	£4.95 (36) £10.60 (96)

PACEF Recommendation

NICE Public Health Guidance (PH10) on smoking cessation services issued in February 2008 makes no specific recommendations as to which type of pharmacotherapy (nicotine replacement therapy (NRT), varenicline or bupropion) is preferred. Choice is dependent on a number of factors including likely compliance, availability of counselling, previous use of cessation therapies, contraindications, adverse effects and patient preference. NICE have also recognised that there may be a need for a combination of different forms of NRT such as patches plus gum, lozenge, inhalator or nasal spray dependant upon the degree of nicotine dependence or previous failed attempts to quit using only single forms of NRT. In support of this agenda and in recognition that Nicorette Fresh Mint Lozenges are comparably priced to alternative formulations, the product is designated GREEN.

REVIEW PRESCRIBING OF DIPIPANONE

There is a recurrent problem, identified to us by Lincolnshire police, of NHS prescribed dipipanone being misused or diverted for illegal purposes. Dipipanone is a strong opioid indicated for moderate to severe pain. It is available as Diconal tablets containing dipipanone 10mg and cyclizine 30mg. In the December Quarter 2010, there were over 300 prescriptions written for more than 22,000 tablets of Diconal in Lincolnshire, with quantities ranging from 4 to 270 tablets per form.

PACEF Recommendation:

Prescribers are strongly advised to review all remaining prescribing of Diconal. As both ingredients have the potential for drug misuse and diversion, Diconal is no longer recommended for prescribing and designated RED-RED. The opioid of choice for moderate to severe pain is oral morphine. For those patients intolerant of morphine, oxycodone can be considered as an alternative. It is illegal to prescribe dipipanone for addiction unless the GP holds a license.

NEW TRIALS IN BRIEF

The ACCORD Study: Long term effects of intensive glucose lowering on cardiovascular outcomes

The ACCORD study investigated the effects of intensive blood glucose lowering in over 10,000 long-standing type 2 diabetics at high cardiovascular (CV) risk. The use of intensive therapy was stopped after 3.7 years due to an increased risk of death (Hazard ratio 1.21; 95% CI 1.02 – 1.44, Number Needed to Harm (NNH) 95), but a lower risk of non-fatal MI. There was no significant difference in the primary

composite outcome (non-fatal MI, non-fatal stroke or CV death) between the intensively treated group (target HbA1c less than 6%) and those who received standard treatment (target HbA1c 7.0 – 7.9%).

This follow up analysis reports the 5 year planned end outcomes after the intensively treated patients were moved to standard therapy (median HbA1c rose from 6.4% at transition to 7.2% at the end of the study). The trends found in the earlier analysis persisted. The use of intensive therapy for 3.7 years increased 5 year mortality, but reduced 5 year non-fatal MIs.

PACEF comment:
This follow up analysis of the ACCORD study confirms an analysis of earlier findings and complements other data (such as the ADVANCE study) which suggest that intensive control of blood glucose in established diabetics is associated with poorer outcomes, including increased mortality. Following a NICE recommendation, QOF Diabetes Mellitus indicator 26 has been revised to reflect the proportion of diabetics achieving an HbA1c of 7.5% (IFCC-HbA1c of 59 mmol/mol) or less (see Quality and Outcomes Framework 2011/12 DM 26).

Reference:
The ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;364: 818 - 828.

DONATION OF PATIENT-RETURNED MEDICINES TO CHARITABLE ORGANISATIONS

PACEF were asked to review the legal and ethical issues surrounding the donation of patient-returned medicines to charities distributing returned medicines to those in need in the developing world.

World Health Organisation, *Guidelines on Drug Donation* (1999).

The standard reference is the *Guidelines on Drug Donation* issued by the World Health Organisation (WHO) in 1999. Although this guidance is now 12 years old it has not been updated.

The main recommendations are:

- All drug donations should be based on expressed need and be relevant to the disease pattern of the recipient country.
- All donated drugs should be approved for use within the recipient country and appear on the national list of essential drugs or on the WHO model list of essential drugs.
- The presentation, strength and formulation of donated drugs should be similar to those drugs commonly used in the recipient country.
- All donated drug should come from a reliable source and comply with quality standards in both the donor and recipient countries.
- **No drugs should be donated that have been issued to patients and then returned to a pharmacy or elsewhere.**
- All drugs received in the recipient country should have a shelf life of at least one year.
- All drugs should be labelled in a language that is easily understood by health professionals in the recipient country.
- As much as possible, donated drugs should be presented in larger quantity units and hospital packs.

Intercare *Statement on Re-use and Re-cycling of Returned Medicines* (revised November 2010)

The charity Intercare has issued their own guidance challenging some aspects of the WHO guidelines. Specifically *they* challenge the statement that patient-returned medicines should not be part of drug donation schemes. They do this on the basis that: (1) use of patient-returned medicines in this way is not illegal (although it is deemed to be unethical by the General Pharmaceutical Council); (2) the WHO statement is outdated and in need of revision; (3) the Code of Ethics for Superintendents and Owners of Pharmacies is not binding on other professions (e.g. dispensing doctors); (4) precedents exist around the re-use of medicines in hospital and the re-use of returned Tamiflu during the recent flu outbreak; (5) it is not prohibited by the Royal College of General Practitioners; (6) advice from PCTs is only guidance and cannot be totally prohibitive on a practice getting involved if they wish; (7) Intercare work hard to ensure the quality and appropriateness of all donations sent to recipient countries.

PACEF Recommendation:
The donation of patient-returned medicines is considered unethical by the General Pharmaceutical Council and should not be undertaken by pharmacists. However, whilst this may be considered as best practice for all healthcare professionals, the Code of Ethics for Superintendents and Owners of Pharmacies is not binding on other professions (e.g. doctors). Nor is the donation of patient-returned medicines prohibited by the Royal College of General Practitioners. As a result of this, GP practices can decide individually as to whether they wish to participate in schemes of this nature. The WHO recommendations provide useful guiding principles on which to evaluate a charity requesting donations of patient-returned drugs. Within this context individual practices could decide to donate relevant patient-returns of sufficiently high quality to reputable charities.

EVALUATION OF THE SCALE, CAUSES AND COSTS OF WASTE MEDICINES

The York Health Economics Consortium and The School of Pharmacy at the University of London have recently completed a large project designed to research all aspects of pharmaceutical waste in England. The key point conclusions from their report are detailed below:

- **The annual cost of NHS primary and community care prescription medicines wastage in England is approximately £300 million per year. This is approximately 4% of the drug spend each year.** This is probably an underestimate as a considerable amount of pharmaceutical waste is disposed of informally through domestic waste and remains unknown to NHS supported pharmaceutical waste collection services.
- Not all wastage is avoidable or occurs as a result of poor practice. **Less than 50% is likely to be preventable.**
- Improving medicines adherence would help to reduce waste and improve health outcomes. This is likely to be a more cost-effective approach than simply attempting to minimise waste in isolation.
- Existing NHS policies to combat waste can be effective including; Medicines Use Reviews (MURs), medication reviews, repeat dispensing and improvement of

prescribing and medicines use processes (using PCT Prescribing and Medicines Management Teams).

- Medicines waste often occurs when repeat medicines accumulate in the patient's home. This can be as a result of: (1) the patient recovering or deteriorating before medicines have been used; (2) treatment being stopped or changed leaving current stock unused; (3) precautionary prescribing linked to palliative care where the treatment provided is never used; (4) poorly controlled repeat prescribing and dispensing processes which allow excessive or poorly coordinated ordering to go unchallenged; (5) poor patient adherence resulting in sub-optimum consumption of prescribed medicines. In extreme cases, the sheer scale of accumulation of repeat medication in the patient's home does not become fully apparent until a healthcare professional gains access to the patient's home or a patient's relative returns a large quantity of medication to the pharmacy or dispensing practice following the patient's final deterioration.
- Opportunities identified for financial saving and improving health outcomes include: (1) targeted support for patients starting new therapies and those on unusually costly and difficult to take treatments; (2) ensuring effective medication review by doctors, pharmacists and, where relevant, other healthcare professionals; (3) encouraging pharmacist managed repeat dispensing (subject to service providers being motivated to prevent unnecessary supply); (4) encouraging 28 day prescribing (there is some evidence that this reduces wastage); (5) focussing on 'treatment resistant' patients who may not be taking their medicines correctly; (6) improving pharmaceutical care for the isolated and vulnerable; auditing supply and use of monitored dosage systems; (7) improving communication on hospital discharge; (8) developing more effective public information campaigns.

PACEF Comment:
A Lincolnshire project utilising many of the principles identified above and supported collaboratively by the PCT Prescribing and Medicines Management Team and practice staff has succeeded in significantly reducing prescribing volume in a Lincolnshire practice with historically high prescribing volume. Practice Based Commissioning Consortia have been asked to nominate further practices with historically high prescribing volume that may be interested in working collaboratively with the P&MMT in the coming months to help address these issues in practice. As projects of this nature are extremely demanding in terms of the amount of time involved, the capacity of the P&MMT to provide this service is extremely limited. Initially only one practice per PBCC should be nominated. Key to the success of this initiative is dedicated support and strong practice commitment to implement and support the necessary changes.

Reference:
York Health Economics Consortium and The School of Pharmacy, University of London, *Evaluation of the Scale, Causes and Costs of Waste Medicines* (November 2010)

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (MARCH 2011)

Modafinil (Provigil): information to support safer use; now restricted to narcolepsy

- The European Medicines Agency (EMA) has recommended that modafinil should only be used to treat excessive sleepiness associated with narcolepsy.
- Use of modafinil to treat excessive sleepiness associated with obstructive sleep apnoea or chronic shift work sleep disorder is no longer advocated.

- Modafinil should **not** be used in those with uncontrolled hypertension or cardiac arrhythmias, children up to 18 years, women who are pregnant or breast feeding.
- Modafinil should be discontinued and not restarted in cases of serious skin or hypersensitivity reactions and psychiatric disorders (e.g. suicidal ideation).
- A baseline ECG should be done before initiation. Patients with abnormal findings require further specialist evaluation.
- CV function (especially BP and heart rate) needs regular monitoring. Modafinil should be discontinued in patients developing arrhythmia or moderate to severe hypertension and should not be restarted until the condition has been adequately evaluated and treated.
- Modafinil should be used with caution in patients with a history of psychosis, depression, mania, alcohol abuse, substance abuse. Such patients should be monitored closely and asked to report any suspected adverse behaviours or thoughts.

PACEF Recommendation (from *PACE Bulletin* Vol 4 No 18 (October 2010)
Modafinil (Provigil) is no longer recommended for excessive sleepiness associated with obstructive sleep apnoea or chronic shift work sleep disorder. It is designated RED-RED for both of these indications. Modafinil remains AMBER for excessive sleepiness associated with narcolepsy. Shared care arrangements are under review.

NICE TECHNOLOGY APPRAISAL 212: *BEVACIZUMAB IN COMBINATION WITH OXALIPLATIN AND EITHER FLUOROURACIL PLUS FOLINIC ACID OR CAPECITABINE FOR THE TREATMENT OF METASTATIC COLORECTAL CANCER* (DECEMBER 2010)

NICE Recommendation

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.

PACEF Recommendation
Bevacizumab intravenous infusion (Avastin) is designated RED-RED for the treatment of metastatic colorectal cancer.

NICE TECHNOLOGY APPRAISAL 214: *BEVACIZUMAB IN COMBINATION WITH A TAXANE FOR THE FIRST-LINE TREATMENT OF METASTATIC BREAST CANCER* (FEBRUARY 2011)

NICE Recommendation

Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer.

PACEF Recommendation
Bevacizumab intravenous infusion (Avastin) is designated RED-RED for the first line treatment of metastatic breast cancer.

NICE TECHNOLOGY APPRAISAL 215: *PAZOPANIB FOR THE FIRST-LINE TREATMENT OF ADVANCED RENAL CELL CARCINOMA* (FEBRUARY 2011)

NICE Recommendation

Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma:

who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 **and**

if the manufacturer provides pazopanib with a 12.5% discount on the list price, and provides a possible future rebate linked to the outcome of the head-to-head COMPARZ trial, as agreed under the terms of the patient access scheme and to be confirmed when the COMPARZ trial data are made available.

PACEF Recommendation:
Pazopanib tablets (Votrient) are designated RED for the first line treatment of advanced renal cell carcinoma.

NICE TECHNOLOGY APPRAISAL 216: *BENDAMUSTINE FOR THE FIRST-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA* (FEBRUARY 2011)

NICE Recommendation

Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

PACEF Recommendation:
Bendamustine (Levact) injection is designated RED for this indication.

NICE CLINICAL GUIDELINE 108: *CHRONIC HEART FAILURE – MANAGEMENT OF CHRONIC HEART FAILURE IN ADULTS IN PRIMARY AND SECONDARY CARE* (AUGUST 2010)

NICE Recommendations

Treatment for heart failure due to left ventricular systolic dysfunction

- Offer both ACE inhibitors and beta-blockers licensed for heart failure as first-line treatment.

Beta-blockers licensed for heart failure

Drug	Licensed indication
Bisoprolol (generic/ Cardicor)	Adjunct in stable moderate to severe heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides
Carvedilol (generic/Eucardic)	Adjunct to diuretics, digoxin or ACE inhibitors in symptomatic chronic HF
Nebivolol (generic/Nebilet)	Adjunct in stable mild to moderate HF in patients over 70 years.

PACEF Recommendation: Beta Blockers

Three beta-blockers are licensed for the treatment of heart failure: bisoprolol, carvedilol and nebivolol. All three are lower cost when prescribed generically. ULHT cardiologists advocate bisoprolol first line.

ACE inhibitors licensed for heart failure

The table below summarizes the licensed indications of ACE inhibitors and Angiotensin 2 receptor antagonists (A2RAs)

Drug name	BP	HF	Post MI prophylaxis	Post MI with LV failure	Diabetic nephropathy Type 1	Diabetic nephropathy Type 2	CV risk reduction
Captopril	√	√	√	√	√		
Cilazepril	√	√					
Enalapril	√	√					
Fosinopril	√	√					
Imidapril	√						
Lisinopril	√	√	√			√	
Moexipril	√						
Perindopril	√	√	√	√			
Quinapril	√	√					
Ramipril	√	√	√	√			√
Trandolapril	√		√	√			
Candesartan	√	√					
Eprosartan	√						
Irbesartan	√					√	
Losartan	√	√				√	√
Olmesartan	√						
Telmisartan	√						√
Valsartan	√	√		√			

Cost of selected licensed ACE inhibitors

	Dose range (HF)	**Cost / 28 days (DT March 2011)**
Enalapril	2.5mg once daily increased gradually to 10-20mg twice daily	£1.10 – £2.46
Lisinopril	2.5 – 35mg once daily	£0.90 – £3.18
Perindopril erbumine (generic)	2 – 4mg once daily	£1.56 – £1.69
Perindopril arginine (Coversyl Arginine)	2.5 – 5mg once daily	£7.71 – £8.74
Ramipril capsules	1.25mg – 10mg once daily	£1.18 –£1.94

PACEF Recommendation: ACE Inhibitors

The ACEIs that are licensed for HF are: captopril, cilazepril, enalapril, fosinopril, lisinopril, perindopril, quinapril and ramipril. Low cost generically available first line options include lisinopril and ramipril. Where perindopril is prescribed it should be prescribed generically as the perindopril erbumine salt and not as the expensive arginine salt (Coversyl Arginine). Perindopril arginine (Coversyl Arginine) is not recommended due to its premium price in comparison to perindopril erbumine (see *PACE Bulletin*, Vol 2, No 3 (April 2008). ULHT cardiologists advocate ramipril first line.

NICE Recommendations (continued)

- Optimise the dose of ACEIs by starting low and titrating upwards at short intervals (e.g. every 2 weeks). Measure serum urea, creatinine, electrolytes and eGFR at initiation and after each dose increment.

PACEF Recommendation: ACEI Dosage in Heart Failure
PACEF are concerned that some patients with HF may not be receiving optimal ACEI treatment in terms of their prescribed dose. Prescribers are urged to ensure that patients with HF have been effectively titrated up to within licensed HF dosage ranges.

NICE Recommendations (continued)

- Offer beta-blockers to all patients including older adults and patients with:

    - peripheral vascular disease
    - erectile dysfunction
    - diabetes mellitus
    - interstitial pulmonary disease
    - COPD without reversibility

- Introduce in a 'start low, go slow' manner and assess heart rate, BP and clinical status after each titration. Switch stable patients already on a beta-blocker for a co-morbidity to a beta-blocker licensed for heart failure (where necessary).
- Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for patients who have intolerable side effects with ACE inhibitors.

Licensed HF doses and cost of HF licensed A2RAs

	Recommended HF titration doses	**Cost for 28 days (DT March 2011)**
Candesartan (Amias) tablets	4mg once daily	£9.78
	8mg once daily	£9.89
	16mg once daily	£12.72
	32mg once daily	£16.13
Losartan (generic) tablets	**12.5mg once daily**	**£7.35**
	25mg once daily	**£1.64**
	50mg once daily	**£1.54**
Losartan (Cozaar) tablets	12.5mg once daily	£8.09
	25mg once daily	£16.18
	50mg once daily	£16.18
Valsartan (Diovan) capsules	40mg twice daily	£27.94
	80mg twice daily	£27.94
	160mg twice daily	£36.82

PACEF Recommendation: A2RAs
A2RAs are only indicated for heart failure in patients unable to tolerate ACEIs. Evidence from studies suggests that ACEI related cough is not as common as often perceived. Concern that the patient may develop an ACEI related cough is not sufficient to justify first line A2RA use. Where an A2RA is indicated, a low cost agent is preferred. ULHT cardiologists advocate losartan or candesartan first line. Generic losartan is currently the lowest cost A2RA by a considerable margin and should be used as the A2RA of first choice for hypertension.

NICE Recommendations (continued)

- If symptoms persist despite optimal first line treatment, seek specialist advice and for second line treatment consider:
    - an aldosterone antagonist licensed for heart failure, especially in moderate to severe heart failure (NYHA class III-IV) or MI in past month or
    - an ARB licensed for heart failure, especially in mild to moderate heart failure (NYHA class II-III) or
    - hydralazine in combination with nitrate, especially in people of African or Caribbean origin with moderate to severe heart failure (NYHA class III-IV).

PACEF Recommendation: Eplerenone

Eplerenone is approved for use post-MI (initiated within 3 to 14 days of the event) for patients with signs and symptoms of heart failure and left ventricular systolic dysfunction. Specialist diagnosis, initiation and intensive initial monitoring are required; renal function and serum potassium should be monitored before and during treatment. Within this context, eplerenone is classified as AMBER, although the routine nature of continued monitoring in primary care does not necessitate a shared care guideline. For patients with clinical heart failure and LVSD already taking spironolactone, treatment can be continued post-MI. Eplerenone represents a better tolerated alternative for those unable to tolerate spironolactone. Within this context it could be initiated by a GP.

NICE Recommendations (continued)

- Digoxin is recommended for worsening or severe HF due to LVSD despite first and second line treatment for HF.
- Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within 8-12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherance.
- The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the therapeutic range.
- Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in patients with HF and titrated (up and down) according to need following the initiation of subsequent HF therapies.
- The diagnosis and treatment of HF with preserved ejection fraction should be made by a specialist and other conditions that present in a similar way may need to be considered. Patients in whom this diagnosis has been made should usually be treated with a low to medium dose of loop diuretics (e.g. less than 80mg furosemide daily). Patients who do not respond to this treatment will require further specialist advice.
- Calcium channel blockers – consider amlodipine for co-morbid hypertension and/or angina but avoid verapamil, diltiazem and short-acting dihydropyridine agents.
- Amiodarone – consult a specialist before offering amiodarone. All amiodarone prescribing should be reviewed regularly. Patients taking amiodarone should have a routine 6 monthly clinical review, including liver and thyroid function test and including a review of side effects.

PACEF Comment:
Shared care arrangements for amiodarone are currently under review and will be covered in a forthcoming issue of the *PACE Bulletin.*

NICE Recommendations (continued)

- Anticoagulants – consider for patients in sinus rhythm with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus.
- Aspirin – offer 75-150mg daily to patients with atherosclerotic arterial disease including CHD.
- Inotropic agents – (e.g. dobutamine, milrinone or enoximone) only consider for the short term treatment of acute decompensation after specialist advice.
- ACE inhibitors – do not initiate in patients with suspected valve disease until assessment by a specialist.

Monitoring

- Include a clinical assessment of functional capacity, fluid status, cardiac rhythm, cognitive status and nutritional status.
- Review drug treatment including need for changes and possible side effects.
- Measure minimum of serum urea, electrolytes, creatinine and eGFR.
- Monitor at short intervals (days to 2 weeks) if the clinical condition or drug treatment has changed, otherwise monitor at least 6 monthly.
- When a patient is admitted to hospital because of heart failure, seek advice on their management plan from a specialist in heart failure.

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