NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 18 **October 2010**

What's new this month:

- **Indacaterol (Onbrez Breezhaler) a new once daily bronchodilator for use in COPD has been designated RED-RED (see page 3)**
- **Finasteride (Proscar) has been approved as the first line 5-ARI of choice in the treatment of benign prostatic hypertrophy; dutasteride (Avodart) and dutasteride/tamsulosin (Combodart) have been temporarily designated RED-RED; criteria for use where finasteride is not tolerated or inappropriate are being developed with local urologists (see page 5).**
- **Sativex Oromucosal Spray, a new treatment for spasticity in patients with multiple sclerosis, has been designated RED-RED (see page 7).**
- **All prescribing of modified release morphine preparations should be by brand name; preferred brands are Morphgesic SR and Zomorph (see page 9)**
- **Calcium supplementation has been associated with an increased risk of myocardial infarction (see page 13)**
- **New shared care guidelines have been developed for hydroxychloroquine in rheumatology and octreotide in acromegaly (see page 15)**
- **Modafinil is no longer recommended for treatment of daytime sleepiness associated with obstructive sleep apnoea syndrome and chronic shift work; it remains approved for the treatment of narcolepsy (see page 15)**

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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.lpct.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: SEPTEMBERY 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Abatacept infusion (Orencia)	Licensed for the treatment of moderate to severe active rheumatoid arthritis	RED
Adalimumab injection (Humira)	Licensed for the treatment of moderate to severe active rheumatoid arthritis	RED
Capecitabine tablets (Xeloda)	Licensed for advanced gastric cancer in combination with a platinum-based regimen	RED
Denosumab (Prolia)	Licensed for the treatment of therapy-induced bone loss in people with non-metastatic prostate cancer	RED-RED
Dutasteride capsules 0.5mg (Avodart)	Licensed for benign prostatic hypertrophy	RED-RED Criteria for use where finasteride is not tolerated or inappropriate are being developed with local urologists. 5-ARIs should only be used in men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men).
Dutasteride/Tamsulosin capsules 0.5mg/0.4mg (Combodart)	Licensed for benign prostatic hypertrophy	RED-RED Criteria for use where finasteride is not tolerated or inappropriate are being developed with local urologists. 5-ARI/alpha blocker combination therapy should only be used in men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30g or a PSA level greater the 1.4ng/ml.
Etanercept injection (Enbrel)	Licensed for the treatment of moderate to severe active rheumatoid arthritis	RED
Finasteride tablets 5mg (Proscar)	Licensed for benign prostatic hypertrophy	GREEN First Line 5-ARI of choice. 5-ARIs should only be used in men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men).
Gefitinib tablets (Iressa)	Licensed for the treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of EGFR-TK.	RED
Imatinib tablets (Glivec)	Licensed for gastrointestinal stromal tumours	RED-RED
Indacaterol (Onbrez Breezhaler)	Licensed for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD)	RED-RED
Infliximab infusion (Remicade)	Licensed for the treatment of active rheumatoid arthritis	RED
Modafinil tablets (Provigil)	Licensed for the treatment of daytime sleepiness associated with narcolepsy Licensed for the treatment of	AMBER RED-RED

	daytime sleepiness associated with obstructive sleep apnoea syndrome Licensed for the treatment of daytime sleepiness associated with chronic shift work	 RED-RED
Morphine sulphate MR tablets (Morphgesic SR)	Licensed for prolonged relief of severe pain	GREEN Prescribe by brand and in preference to MST Continus.
Morphine sulphate MR capsules (Zomorph)	Licensed for severe chronic pain	GREEN Prescribe by brand and in preference to MST Continus.
Rituximab infusion (MabThera)	Licensed for previously untreated or relapsed chronic lymphocytic leukaemia Licensed for severe active rheumatoid arthritis	RED RED
Sativex Oromucosal Spray	Licensed as an add-on treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication.	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 within licensed indications**. Specialist initiation and shared care guidelines are not considered necessary.

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.**

NEW DRUG ASSESSMENT: INDACATEROL (ONBREZ BREEZHALER)

Indacaterol (Onbrez) is the first once-daily inhaled long acting beta-2 agonist (LABA). It is licensed for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD); it is not currently licensed for the treatment of asthma. Indacaterol is administered as 150 microgram or 300 microgram capsules inhaled through a dry powder inhaler device known as the Breezhaler.

PACEF reviewed three randomised controlled trials (RCTs) conducted in adults with moderate to severe COPD. In the INLIGHT study, indacaterol in a dose of 150 microgram was shown to be superior to placebo. In two comparative studies, INVOLVE and INHANCE, indacaterol was found to be at least as effective as formoterol (at a dose of 12 microgram twice daily) and once daily tiotropium (18 microgram twice daily). However, all three trials can be criticised for using short-term disease orientated outcomes (such as change to FEV_1) as primary outcome measures. The longest of the trials was for 52 weeks (INVOLVE) and so concerns remain around the lack of long term safety and efficacy data. A Scottish Medicines

Consortium (SMC) review of the trials highlights inconsistent results for indacaterol in terms of time to first exacerbation and days of poor control.

In all studies the overall incidence of adverse events was similar for the active treatment and the placebo groups. The most common adverse events recorded for indacaterol at licensed doses were: nasopharyngitis (9%), cough (7%), upper respiratory tract infection (6%) and headache (5%). Long term safety remains unknown.

NICE have recently published their Clinical Guideline 101 on the *Management of COPD in primary and secondary care* (June 2010) and have concluded that for patients requiring regular maintenance inhaled therapy with a $FEV_1 \geq 50\%$, either a LABA or a long acting muscarinic antagonist (e.g. tiotropium) should be used. A cost comparison reveals that the least costly treatment option from the range now available would be the formoterol Easyhaler; formoterol Modulite represents a reasonably priced alternative formulation. Indacaterol Breezhaler has been priced competitively with another premium priced LABA, salmeterol (Serevent) Evohaler, although both are expensive in comparison to formoterol. Even premium priced LABAs are lower in cost than tiotropium:

Drug	Daily dose range	Cost (£)pa
Tiotropium Respimat®	5mcg OD	£441
Tiotropium Handihaler®	18mcg OD	£424
Indacaterol Breezhaler®	150 or 300mcg OD	£356
Salmeterol Evohaler®	50mcg BD	£356
Formoterol Turbohaler®	12mcg BD	£302
Formoterol caps for inhaln.	12mcg BD	£284
Formoterol Modulite®	12mcg BD	£219
Formoterol Easyhaler®	12mcg BD	£144

PACEF Recommendations

PACEF are keen to ensure that new NICE Clinical Guidelines on the treatment of COPD are followed. According to NICE, there is a role for LABA treatment in patients with COPD with a $FEV_1 \geq 50\%$ predicted who require regular maintenance inhaled therapy. Indacaterol (Onbrez Breezhaler) is the third LABA to come to market and the first to provide a once daily treatment option. However, none of the three RCTs reviewed provided evidence of long term safety or long term efficacy and all were focused on disease orientated outcomes rather than patient orientated outcomes. Evidence from these trials is promising, but was insufficient to gain PACEF support at this stage. In addition, the premium price of the product (Onbrez Breezhaler is 2.5 times the cost of formoterol Easyhaler and comparably priced to the Serevent Evohaler) mitigates against its first line use. NICE have also identified a role for LABA/Inhaled corticosteroid (ICS) combination inhalers in patients with COPD with a $FEV_1 \leq 50\%$ predicted who require regular maintenance inhaled therapy. Indacaterol is not currently available in a combination inhaler, although a mometasone/indacaterol combination is in development. Following this deliberation, indacaterol (Onbrez Breezhaler) is designated RED-RED subject to review.

NEW DRUG ASSESSMENT: DUTASTERIDE 0.5MG CAPSULES (AVODART) AND DUTASTERIDE/TAMSULOSIN 0.5MG/0.4MG CAPSULES (COMBODART)

Dutasteride is a 5-alpha reductase inhibitor (5-ARI) licensed for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). It is currently available both as monotherapy (Avodart) and in combination with tamsulosin (Combodart). The only competing 5-ARI in the market place is finasteride (Proscar) also licensed for BPH. PACEF reviewed the evidence for all three products in order to determine which 5-ARI should be used first line and whether there was any advantage to the Combodart combination.

The Evidence

Evidence for dutasteride in the treatment of BPH originally came from a pooled analysis of the results from three identical placebo controlled trials which demonstrated improvements in symptom control and an absolute risk reduction in incidence of acute urinary retention (AUR) of 2.4%. Supporting evidence for the use of Combodart, the dutasteride/tamsulosin combination product, comes from one published study: CombAT. Results concluded that combination therapy (dutasteride plus tamsulosin) proved significantly superior to each component used as monotherapy in terms of symptom improvement. Superiority of the combination product versus dutasteride alone was significant at 3 months and versus tamsulosin alone was significant at 9 months. The benefits of the combination therapy were associated with continuing improvement for up to 2 years. Evidence for finasteride comes from a large multicentre RCT which showed that either as monotherapy or in combination with doxazosin, finasteride is effective at preventing the progression of BPH and reducing the risk of AUR.

The mechanism of action of both 5-ARIs is similar, although dutasteride inhibits both isomer forms of the enzyme 5-alpha reductase whereas finasteride is only effective against one. Theoretically, dutasteride should be expected to provide greater suppression of dihydrotesterone, although published comparative data is limited and inconclusive. The one published comparative study, EPICS, showed no statistical difference between the two treatments in terms of symptom control and reduction in prostate volume. A retrospective analysis of placebo controlled trials for both drugs indicates that dutasteride is slightly more effective in terms of reduction in episodes of acute urinary retention (AUR) and BPH related surgery. However, whilst indicating possible trends and suggesting areas for further research, currently available data is insufficiently robust to provide conclusive evidence that one product is superior to the other in terms of efficacy.

Adverse effects between both 5-ARIs are similar although there appears to be more of a risk of male breast cancer associated with finasteride use than compared with dutasteride. The MHRA issued a warning on the possible association of finasteride and the incidence of male breast cancer in December 2009 (see *PACE Bulletin* Vol 4 No 1 (January 2010)). There is currently no conclusive evidence of any causal association between dutasteride and male breast cancer.

The Guidance

NICE Clinical Guideline G97: *Lower urinary tract symptoms – The management of lower urinary tract symptoms (LUTS) in men* was published in May 2010. Lower Urinary Tract Symptoms (LUTS) is an umbrella term introduced 15 years ago to dispel the perception that all urinary symptoms that arise in the male are associated

with the prostate. NICE CG 97 is the first national guideline to acknowledge this and to avoid using the term BPH. The Guideline places particular emphasis on a thorough initial assessment of all patients and places conservative management of symptoms including bladder training, the use of incontinence products and appliances, before drug treatment.

Alpha blockers (e.g. alfuzosin, doxazosin, tamsulosin or terazosin) are recommended as first line treatment in men with moderate to severe LUTS but with normal prostates. According to NICE, 5-ARIs should be offered to men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men). This is based on evidence from RCTs that men with higher risk of progression (such as older men with poorer flows, higher symptom scores, greater residuals, larger prostates and higher PSAs) are more likely to benefit from 5-ARIs than men with normal prostates. NICE have also conducted a review of the economic evidence and have concluded that alpha blockers are more cost-effective in the normal prostate group; the cost effectiveness of 5-ARIs improves in the higher risk of progression group defined above. NICE has not differentiated clinically between the two currently licensed 5-ARIs.

The combination of alpha blockers and 5-ARIs has been shown to be more effective than either drug used alone as evidenced by the results of the CombAT study reported above. Treatment with alpha blockers may result in observable symptom improvements in 4-6 weeks whereas benefits associated with a 5ARI alone may require up to 6 months treatment. As a result of this, NICE have recommended combination alpha blocker and 5-ARI treatment in men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30g or a PSA level greater the 1.4ng/ml. 5-ARI and 5-ARI/alpha blocker combination therapy is unlikely to be cost-effective outside of this context.

<u>The Cost</u>

A cost comparison of the two 5-ARIs reveals the following:

Drug	**Daily dose range**	**Cost per pack**	**Cost (£)pa**
Dutasteride capsules 0.5mg (Avodart)	`0.5mg daily	£19.80 (30)	£240.24
Finasteride tablets 5mg (generic)	**5mg**	**£2.71 (28)**	**£35.23**
Finasteride tablets 5mg (Proscar)	5mg	£13.94(28)	£181.22

<u>PACEF Recommendations: Finasteride vs Dutasteride</u>
PACEF has evaluated the clinical evidence for both finasteride and dutasteride in the treatment of BPH and can find no compelling evidence of one treatment being superior to another. NICE have conducted a similar review and have also failed to find reason to differentiate clinically between the two 5-ARIs. As a result of this, finasteride is approved as the first line 5-ARI of choice; it should be prescribed generically to avoid the high cost of branded Proscar. As a result of this, generic finasteride tablets 5mg are designated GREEN. All new 5-ARI initiations should be for finasteride; any existing Proscar prescribing should be switched to generic finasteride. All patients prescribed finasteride should be made aware of the risk of male breast cancer and advised to promptly report any changes in breast tissue (e.g. lumps, pain or nipple

discharge) to their doctor. Dutasteride (Avodart) has been designated RED-RED and new initiations should cease. Criteria defining a potential role in patients intolerant to or inappropriate for finasteride are being developed with local urologists. Therapeutic switching from dutasteride to finasteride is encouraged where finasteride is appropriate for use, but has never previously been prescribed. Support from the Prescribing and Medicines Management Team is available for practices wishing to undertake this switch. 5-ARIs should only be prescribed as designated by NICE (i.e. for men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men)).

A cost comparison of Combodart and alternative 5-ARI/alpha blocker combinations prescribed as separate components reveals the following:

Drug	Daily dose range	Cost per pack	Cost (£)pa
Combodart (dutasteride + tamsulosin)	1 capsule daily (0.5mg + 0.4mg)	£19.80 (30)	£240.24
Dutasteride + tamsulosin	0.5mg +400mcg m.r	£19.80 + 4.84	£298.96
Finasteride + doxazosin m.r	**5mg + 4mg**	**£2.71 + £5.70**	**£109.33**
Finasteride + doxazosin m.r	**5mg + 8mg**	**£2.71 + £9.98**	**£164.97**
Finasteride + tamsulosin	**5mg + 400mcg**	**£2.71 + £4.84**	**£93.95**

PACEF Recommendation: Combination 5-ARI/Alpha Blocker Therapy
5-ARI/alpha blocker combination therapy is acknowledged to be more effective than monotherapy, but, due to concerns over cost-effectiveness, should be reserved for men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men). Finasteride is confirmed as the 5-ARI of choice and combination therapy should usually involve combination of finasteride with a separate alpha blocker such as generic doxazosin or tamsulosin. Dutasteride/alpha blocker combination therapy is designated RED-RED and new initiations should cease. Criteria defining a potential role in patients intolerant to or inappropriate for finasteride are being developed with local urologists.

NEW DRUG ASSESSMENT: SATIVEX OROMUCOSAL SPRAY

Sativex is a cannabis-based medicine formulated as an oromucosal spray. It has been available unlicensed since December 2005 and has recently been launched as a licensed product in the UK. Sativex is licensed as an add-on treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication.

PACEF reviewed the main supporting evidence which comes from one phase 3 trial, the results of which have yet to be fully published. 572 patients with MS were enrolled in a 4 week single blind run-in period to determine if they were responsive to Sativex. 272 pts (48%) had ≥20% reduction in spasticity scores and were classified as responders. Of these, 241 were then enrolled in the 12 week double-blind phase of the trial. The average age of study participants was 48.5 years and 60% were

female. The average duration of MS was 12.14 years with spasticity for just over 7 years. Patients were randomised to receive either Sativex (124 pts) or placebo (117pts). The mean dose of Sativex was 8.3 sprays/day. The response was monitored using a spasticity rating score with 0=none and 10=worst. Patients were also taking a variety of background medication including baclofen (57%), tizanidine (19%), benzodiazepines (17%), others (gabapentin, dantrolene and botulinum) (12%) and disease modifiers (53%). The results of the trial showed that Sativex improved spasticity and reduced sleep disturbances more effectively than placebo as measured by changes to the spasticity scores.

However, PACEF had many concerns with the trial design:

- The two stage structure to the study excluded known Sativex non-responders from the second stage. This will have resulted in a bias toward Sativex in the second stage placebo controlled RCT.
- Patients were also taking a variety of background medication, including many alternative treatments for spasticity. This will have confounded and contaminated the results.
- The trial was of short duration and MS is a long term condition. There is no evidence of long-term efficacy or safety of Sativex.
- No comparative studies of Sativex against other treatments for spasticity exist.
- The patient responses within the trial were reported in terms of patient/physician/carer perception of improvement in symptoms as determined by various spasticity rating scores. The clinical significance of these subjective assessments of improvement is not clear.
- Secondary outcomes such as benefits in daily living were reported in terms of difference compared to the placebo group; insufficient information is available to determine whether these improvements are of clinical significance.

The most common adverse effects associated with the use of Sativex are dizziness, fatigue, somnolence, nausea, dry mouth, urinary infection, vertigo and sore mouth. The required dose is anything from one to 12 sprays daily with at least a 15 minute gap required between each dose. Patients requiring higher doses may find this problematic. Treatment should only be initiated by a specialist and requires careful titration of dose for each individual.

Sativex is significantly more expensive than any alternative treatment listed in current NICE guidance:

Drug	**Daily dose range**		**Cost (£)pa**
Sativex	**Up to 12 sprays a day. Normal range 8-12 sprays a day**	**£125 (10ml) 90 actuations**	**£4,062 – £6,061 pa.**
baclofen	3mg three times day max dose 100mg	£1.96 (84 x 10mg)	£84.93 (max dose 100mg/day)
gabapentin (not licensed)	900-2700mg daily in divided doses	£4.99 (100X300mg caps) £29.08 (100 x 600mg tabs)	£ 54.49-£372.04 (600mg – 2700mg/ day)
tizanidine	2mg increased to 24mg daily Max 36mg daily	£ 8.63(120 x 2mg) £12.39(120 x 4mg)	£225.50 - £338.25 (24mg-36mg/day)
diazepam	2-15mg, max 60mg daily	£1.10(28 x 2mg) £1.12(28 x 5mg) £1.14(28 x 10mg)	£14.30-£88.92 (2mg-60mg/day)
dantrolene	25mg daily increased to 100mg qds.	£16.87 (100 x 25mg) £43.07 (100 x 100mg)	£552.66-£672.10 (75mg tds-100mg qds)

PACEF Recommendation:
PACEF were unconvinced by the limited evidence currently available and were unable to approve Sativex Oromucosal Spray for use in NHS Lincolnshire. Designation: RED-RED.

REVIEW: MODIFIED RELEASE ORAL MORPHINE SULPHATE PREPARATIONS

NHS Lincolnshire spends in excess of £0.3M p.a. on modified release oral morphine preparations. Most of this expenditure can be attributed to the premium priced brand leader product, MST Continus tablets, despite the fact that much of our prescribing from modified release morphine is generic. This is because, the *Drug Tariff* dictates that when morphine sulphate MR tablets are prescribed generically the dispenser is reimbursed the price of MST Continus (i.e. it is a category C product in part VIII of the *Drug Tariff*). This means that practices, Clusters and the PCT are being charged for a premium priced branded product even when a lower cost product is being supplied.

It has been estimated that specifying a lower cost brand of morphine sulphate MR tablets/capsules rather than prescribing generically could generate cost savings across Lincolnshire of approximately £100K p.a.

Which modified release morphine formulation?

There are two alternatives to MST Continus tablets, Morphgesic MR tablets and Zomorph MR capsules. A cost comparison reveals the following:

	MST	Morphgesic	Zomorph
5mg	£3.29	-	-
10mg	£5.16	£3.85	£3.47
15mg	£9.61	-	-
30mg	£12.40	£9.24	£8.30
60mg	£24.20	£18.04	£16.20
100mg	£38.30	£28.54	£25.65
200mg	£76.62	-	£51.30

Prices compiled from *MIMS*, August 2010

The table illustrates that both products are significantly lower in price than MST and are available in all of the key strengths.

Morphgesic tablets

	Pros	Cons
Available strengths	Available in four strengths (10mg, 30mg, 60mg, 100mg)	Lower strengths (5mg and 15mg) and 200mg are not available.
Appearance	Tablet colour and packaging resemble MST Continus	
Generic prescribing		Generic prescribing will result in the MST Continus reimbursement price being paid.
Bioequivalence	Morphgesic tablets have been shown to be bioequivalent with MST Continus	
Interface issues		Morphgesic tablets are not used within ULH

Zomorph capsules

	Pros	Cons
Available strengths	Available in five strengths (10mg, 30mg, 60mg, 100mg and 200mg)	Lower strengths (5mg and 15mg) are not available.
Appearance		Does not resemble MST Continus
Generic prescribing		Risk of confusion with MXL once daily capsule if prescribed generically
Bioequivalence	Zomorph capsules have been shown to be bioequivalent with MST Continus	
Interface issues	Zomorph capsules is the MR morphine formulation of choice within ULH	
Swallowing difficulties	Zomorph capsules can be opened and the contents sprinkled onto a spoonful of semi-solid food (e.g. yoghurt) or used to make a suspension that can be administered via a gastric or gastronomy feeding tube.	

PACEF Recommendation
Having reviewed the evidence for both alternative MR morphine preparations, PACEF is not inclined to advocate one preparation over another. Consequently, both Morphgesic and Zomorph are designated GREEN. Prescribers are urged to ensure that all new MR morphine prescribing should specify either Morphgesic or Zomorph by brand depending on prescriber preference or the needs of the patient. Where possible, existing MR morphine prescribing should be standardized around branded Morphgesic or Zomorph, although it is acknowledged that some residual MST Continus prescribing will need to remain, particularly where strengths only available in the MST Continus range are in use.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 191: CAPECITABINE FOR THE TREATMENT OF ADVANCED GASTRIC CANCER (JULY 2010)

Capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer.

PACEF Recommendation
Capecitabine tablets (Xeloda) are designated RED for the treatment of advanced gastric cancer in combination with a platinum based regimen.

NICE TECHNOLOGY APPRAISAL 192: *GEFITINIB FOR THE FIRST-LINE TREATMENT OF LOCALLY ADVANCED OR METASTATIC NON-SMALL-CELL LUNG CANCER* (JULY 2010)

Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small cell lung cancer if: (1) they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and: (2)

the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

PACEF Recommendation
Gefitinib (Iressa) tablets are designated RED for the treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of EGFR-TK.

NICE TECHNOLOGY APPRAISAL 193: *RITUXIMAB FOR THE TREATMENT OF RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKAEMIA* (JULY 2010)

Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory chronic lymphocytic leukaemia except when the condition:

- is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6months of treatment) or
- has previously been treated with rituximab (unless in the context of a clinical trial)

Rituximab in combination with fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab.
Rituximab in combination with chemotherapy other than fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia.

PACEF Recommendation
Rituximab infusion (MabThera) is designated RED for the treatment of relapsed or refractory chronic lymphocytic leukaemia.

NICE TECHNOLOGY APPRAISAL 194: *DENOSUMAB FOR THE TREATMENT OF THERAPY-INDUCED BONE LOSS IN NON-METASTATIC PROSTATE CANCER* (TERMINATED APPRAISAL) (JULY 2010)

NICE is unable to recommend the use of denosumab for the treatment of therapy-induced bone loss in people with non-metastatic prostate cancer because no evidence submission was received from the manufacturer or sponsor of the technology.

PACEF Recommendation
Denosumab (Prolia) is designated RED-RED for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. A New Drug Assessment is in development designed to assess denosumab (Prolia) for the prevention of osteoporosis in postmenopausal women at increased risk of fracture. Further guidance will be issued by PACEF later in the year.

NICE TECHNOLOGY APPRAISAL 195: *ADALIMUMAB, ETANERCEPT, INFLIXIMAB, RITUXIMAB AND ABATACEPT FOR THE TREATMENT OF RHEUMATOID ARTHRITIS AFTER THE FAILURE OF A TNF INHIBITOR* (AUGUST 2010)

Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.

Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following re-treatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more.

Treatment should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of RA.

[This position on rituximab largely reiterates the existing NICE position from TA126 *Rituximab for the treatment of rheumatoid arthritis* (August 2007)]

Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.

Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event.

Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

A team experienced in the diagnosis and treatment of rheumatoid arthritis and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab, adalimumab, etanercept, infliximab or abatacept.

PACEF Recommendation

Rituximab (MabThera) is designated RED for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade) and abatacept (Orencia)

are also designated RED for this indication subject to criteria. Abatacept (Orencia) was previously designated RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL 196: *IMATINIB FOR THE ADJUVANT TREATMENT OF GASTROINTESTINAL STROMAL TUMOURS* (AUGUST 2010)

Imatinib is not recommended for the adjuvant treatment of gastrointestinal stromal tumours (GISTs) after surgery. People currently receiving imatinib for the adjuvant treatment of gastrointestinal stromal tumours after surgery should have the option to continue treatment until they and their clinician consider it appropriate to stop.

PACEF Recommendation
Imatinib tablets (Glivec) are not recommended for the adjuvant treatment of gastrointestinal stromal tumours (GISTs) after surgery and are designated RED-RED for this indication.

NEW TRIALS IN BRIEF

BMJ META-ANALYSIS OF CALCIUM SUPPLEMENTS AND RISK OF MI AND CV EVENTS

Reference: Bolland MJ et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis *BMJ* 2010; 341:c3691

The *British Medical Journal* (BMJ) has published a meta-analysis of RCTs that identifies a 30% increase in the relative risk of myocardial infarction associated with calcium supplements compared with placebo. Increases in strokes and death were not statistically significant. This study has been widely reported in the general media and has raised some concern among GPs around the apparent risk to patients currently taking calcium and vitamin D supplements.

About the study

The meta-analysis found 15 trials that met the inclusion criteria. These were:

- Double blind, randomised placebo controlled trials of calcium supplementation (at least 500mg elemental calcium) of at least one years' duration.
- Participants aged more than 40 years.
- 100 or more participants

Studies of calcium and vitamin D were specifically excluded unless vitamin D was administered to both arms of the study; this applied to just one study in the 15 analysed.

The original study authors were asked to supply patient level data. Of the 15 trials that met the inclusion criteria, patient level data was supplied for 5 trials (total 8,151 participants, median follow up 3.6 years) and trial level data was available from these plus 6 further studies (11,921 participants, mean duration 4 years). Cardiovascular outcomes were obtained in a non-standardised way from self-reports, hospital admissions and death certificates. The primary outcomes of the meta-analysis were time to first myocardial infarction, first stroke and time to a composite of first MI, stroke or sudden death. The secondary outcome was all cause mortality.

Results

Patient level data (6 trials)

Outcome	**Calcium (n= 4097)**	**Placebo (n=4054)**	**Hazard ratio**
MI	143	111	1.31(95% CI 1.02 to 1.67, P=0.035)
Stroke	167	143	1.20 (95% CI 0.96 to 1.50, P=0.11) Not statistically significant
MI, stroke or sudden death	293	254	1.18 (95% CI 1.00 to 1.39, P=0.057) Not statistically significant
Death	519	487	1.09 (95% CI 0.96 to 1.23, P=0.18) Not statistically significant

Trial level analysis (11 trials)

The results are broadly similar.

Outcome	Calcium group (n= 6116)	Placebo (n=5805)	Hazard ratio
MI	166	130	1.27 (95% CI 1.01 – 1.59)
Stroke	212	190	Not statistically significant
MI, stroke or sudden death	358	319	Not statistically significant
Death	559	535	Not statistically significant

Numbers needed to harm (NNH)

Using the figures reported in the 11 trial analysis:

There were 166 MIs among 6116 participants taking calcium (absolute risk 2.71%)
There were 130 MIs among 5805 participants taking placebo (absolute risk 2.24%)

Absolute risk increase = 0.47% NNH = 100/0.47 = 212.7

If 213 people are treated with calcium instead of placebo for a period of 4 years 1 will be caused to have an MI.

Discussion

This study raises questions over the use of calcium supplements alone to reduce osteoporotic fractures. **The results of this study cannot be extended to the use of calcium and vitamin D supplements but inevitably raise questions about the safety of co-administered calcium and vitamin D.**

In an attempt to address this issue, the National Prescribing Centre (NPC) (in a review of this study) refer to a meta-analysis of 18 RCTs of vitamin D supplementation versus control which reported that vitamin D reduced all cause mortality (RR 0.93, 95% CI 0.87 – 0.99). Furthermore, risk reductions were similar in the trials which did and did not include calcium supplements. It is therefore possible that the addition of vitamin D mitigates any harmful effects of calcium supplementation.

PACEF Recommendations

(1) Calcium supplementation (without vitamin D) is known to have only modest effects on bone density and, given that this data suggests evidence of harm, calcium supplementation alone should not be used in the management of osteoporosis.

(2) People using calcium supplements (without vitamin D) to improve bone health should be advised to use dietary change to ensure an adequate intake of calcium or consider the use of supplements containing both calcium and vitamin D.

(3) The results of the study do not extend to the use of calcium and vitamin D supplements. Other studies have reported that calcium and vitamin D does not increase the risk of CV events and a meta-analysis of vitamin D RCTs suggests that vitamin D may reduce all cause mortality.

SHARED CARE GUIDELINES

Two new shared care guidelines have been approved for use:

- Hydroxychloroquine in Rheumatology
- Octreotide for the treatment of acromegaly

Both SCGs will be available through the NHSL website and from specialist services wishing to instigate shared care for these patients. Any queries or problems relating to shared care should be addressed to Cathy Johnson, Interface Lead Pharmacist at: cathy.johnson@lpct.nhs.uk

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (AUGUST 2010)

Modafinil: European Medicines Agency recommends restricted use

- The 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.

PACEF Recommendation

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.

Topical ketoprofen: reminder on risk of photosensitivity reactions

- Healthcare professionals are reminded of the risk of photosensitivity reactions with topical ketoprofen.
- Patients should ensure that treated areas are protected from sunlight during the whole period of topical ketoprofen treatment and for 2 weeks after stopping treatment. Careful handwashing after every application is advocated.
- Patients should stop treatment immediately if they develop any skin reaction after application of topical ketoprofen.

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