Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

Volume 2; Number 6 **May 2008**

CONTENTS

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. Steps will be taken to ensure the widest possible distribution across Lincolnshire PCT and within United Lincolnshire Hospitals Trust and Lincolnshire Partnership Trust. Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, care pathways and other PACEF publications available through the LPCT website.

SUMMARY OF PACEF DECISIONS: MARCH UPDATE

Drug	Indication	Traffic Light Status
Actonel Combi (Risedronate 35mg tablets plus calcium 1000mg and vitamin D3 granules 880IU)	**Treatment of postmenopausal osteoporosis in assessed patients for whom the amount of calcium and vitamin D3 included is considered to provide adequate supplementation.**	**RED-RED**
Cozaar-Comp tablets (Losartan plus hydrochlorothiazide) 100mg/12.5mg, 100mg/25mg, 50mg/12.5mg	**Hypertension in patients whose BP is not controlled by hydrochlorothiazide or losartan monotherapy. Reduction in risk of stroke in hypertensive patients (except black patients) with left ventricular hypertrophy**.	**RED-RED**

Fosavance tablets (Alendronate 70mg plus vitamin D3 2800IU) tablets	**Treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency**	**RED-RED**
Ketoconazole (Nizoral)	**Treatment of dermatophytosis and Malassezia folliculitis that cannot be treated topically because of the site, extent of the lesion, or deep infection of the skin resistant to, or in patients intolerant of, fluconazole, terbinafine and itraconazole.** **Treatment of chronic mucocutaneous candidosis, cutaneous candidosis and oropharyngeal candidosis that cannot be treated topically because of the site, extent of the lesion, or deep infection of the skin, resistance to, or in patients intolerant of, both fluconazole and itraconazole.**	**RED** **Treatment should be initiated by a physician experienced in the management of fungal infections; in the majority of cases it would be reasonable to expect the full course to be provided and monitored from secondary or tertiary care**
Retapamulin 1 % ointment (Altargo)	**Licensed for superficial skin infections (including impetigo), infected lacerations, abrasions and sutured wounds**	**RED-RED**
Rituximab (MabThera) infusion	**Relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma**	**RED**
U-500 Insulin injection (Humulin R)	**Unlicensed**	**RED**

RED-RED: This signifies that a product is **not recommended** for prescribing in **both** primary and 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 ULHT and/or LPT **only** and has **no role in primary 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; in the coming months PACEF will be working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. Specialist initiation and shared care guidelines are not considered necessary.

NEW DRUG ASSESSMENTS

RETAPAMULIN OINTMENT 1% (ALTARGO)

Retapamulin ointment 1% (Altargo) is a new topical antibacterial preparation licensed for the short term treatment of superficial skin conditions such as impetigo and infected small lacerations, abrasions and sutured wounds. It is expensive compared to alternative preparations as illustrated by the following cost comparison:

Product	Licensed Indication	Price
Retapamulin 1 % ointment (Altargo)	**Superficial skin infections including impetigo, infected lacerations, abrasions and sutured wounds.**	**5g £7.89**
Neomycin 0.5% cream	Bacterial skin infections	15g £4.39
Fucidin 2 % cream Sodium fusidate	Bacterial skin infections	15g £2.00
Bactroban 2% ointment mupirocin	Primary skin infections	15g £4.38

The most recent PACEF guidance on the treatment of impetigo appears in *Guidance on the Use of Antibacterial Drugs in Lincolnshire Primary Care: Winter 2007/8*. The recommended first line treatment for impetigo is oral flucloxacillin or erythromycin; if topical treatment is required, a five day course of sodium fusidate 2% cream is advocated. Health Protection Agency advice states that, due to increasing resistance, topical antibiotics should be reserved for very localized lesions. Additionally, retapamulin ointment should not be used to treat infections known or thought to be due to methicillin resistant staphylococcus aureas (MRSA) as clinical studies have failed to show sufficient efficacy. It is also not recommended in the treatment of abscesses.

PACEF Recommendation:
PACEF are concerned about the link between the use of topical antibacterial agents and increasing resistance and endorse the position that topical preparations have a very limited role in current therapy. Retapamulin ointment (Altargo) is also an expensive agents in comparison to alternatives. Retapamulin ointment is designated RED-RED.

ACTONEL COMBI

Actonel Combi is a combination pack licensed for the treatment of postmenopausal osteoporosis containing 4 tablets of the bisphosphonate, risedronate sodium 35mg, and 24 sachets of calcium (100mg) and vitamin D (880 IU) granules. Proctor and Gamble, the manufacturer of the product, claim that results from 200 face-to-face interviews show that 72% of patients prefer combination packaging over separate components; the same survey showed that 80% found the dosage instructions for the combination pack easier to understand than instructions on the separate packs.

A cost comparison of Actonel Combi and risedronate 35mg (Actonel) reveals that the products are the same price. The calcium and vitamin D3 sachets provided with the product contain evidence based doses of calcium and vitamin D3 at no additional cost. However, our first line recommended bisphosphonate of choice, generic weekly alendronate, is significantly lower in cost than Actonel Combi even when calcium and vitamin D is prescribed concurrently. The patent for risedronate is due to expire in 2010.

Product	**Licensed Indication and Recommended Dosage**	**Cost of 28 Days Treatment**
Actonel Combi risedronate 35mg + calcium and vitamin D_3 granules 1000mg/880IU	Treatment of postmenopausal osteoporosis in assessed patients for whom the amount of calcium and vitamin D3 included is considered to provide adequate supplementation. One tablet a week plus contents of one sachet on the other six days of the week.	Actonel tabs 35mg x 4 Calcium/Vit D_3 sachets x 24 1x28 day pack £20.30
Risedronate 35mg tabs (Actonel)	Treatment of postmenopausal osteoporosis. One tablet a week.	£20.30
Alendronate 70mg tabs	Treatment of postmenopausal osteoporosis. One tablet a week.	£4.12

PACEF Recommendation:
PACEF found the small scale interview based study presented as an evidence base for Actonel Combi to be insufficient to justify its use. The first line preferred bisphosphonate advocated both locally and in draft NICE guidance is weekly generic alendronate 70mg, usually prescribed concurrently with an appropriate calcium and vitamin D formulation. Risedronate should be reserved for second line use where alendronate is contraindicated or poorly tolerated. Where concurrent calcium and vitamin is indicated it should be prescribed separately in evidence based doses (see below). PACEF acknowledge that this will be more expensive than Actonel Combi in the short term, but would rather avoid combination therapy at this stage rather than disrupt patients by asking them to switch to separate risedronate and calcium and vitamin D when the Actonel patent expires in 2010. As a result of this Actonel Combi is designated: RED-RED.

CALCIUM AND VITAMIN D SUPPLEMENTATION

NICE Technology Appraisal 87 considers the use of bisphosphonates in the secondary prevention of osteoporotic fragility fractures in postmenopausal women and concludes that **all women receiving osteoporosis treatment should receive calcium and vitamin D supplementation** unless clinicians are confident that patients have an adequate intake of calcium and are vitamin D replete[1].

Additionally, **there is evidence to suggest that calcium and vitamin D reduces the risk of fracture in elderly institutionalised patients**. In 1992, Chapuy and colleagues, publishing in the *New England Journal of Medicine*, reported on 3270 elderly women (mean age 84 +/- 6 years) living in sheltered accommodation or nursing homes who were given **1200mg of calcium and 800iu of vitamin D daily** for 3 years. Over this period, the relative risk of hip fracture was reduced by 43% and non-vertebral fracture by 32%[2]. A Cochrane Systematic Review published in 2006 concluded that vitamin D with calcium reduced hip fractures and non-vertebral fractures, but could find no evidence of effect on vertebral fractures; these benefits were again confined to those living in institutional care[3]. A recent study by Porterhouse and colleagues published in

the *British Medical Journal* showed that these benefits did not extent to primary prevention in community dwelling older women at increased risk of hip fracture[4].

NICE Clinical Guideline 21, entitled *The assessment and prevention of falls in older people* (November 2004), revealed emerging evidence that correction of vitamin D deficiency or insufficiency may reduce propensity for falling. However, NICE concluded that there was insufficient evidence to recommend vitamin D supplementation to reduce the risk of falls[5]. More evidence to support the use of calcium and vitamin D to reduce falls has emerged since this CG was published. A meta-analysis of vitamin D supplementation in five relatively short-term randomised controlled trials suggested a 20% reduction in falls among ambulatory or institutionalised individuals[6]. The Royal College of Physicians clinical guideline for the management of osteoporosis includes an algorithm that advocates use of calcium and vitamin D for frail patients at increased risk of falling[7]. The Lincolnshire Falls Service has also used this reference to support their recommendations to use calcium and vitamin D.

The evidence base for managing steroid induced osteoporosis is not strong. The Royal College of Physicians guidelines in 2002 suggest that **all patients on long-term oral steroids should have an adequate intake of calcium and vitamin D[8]**.

Only calcium and vitamin D formulations containing an evidence based dose of each component should be prescribed (i.e. 1200mg of calcium and 800i.u. of vitamin D daily). The table below lists all of the key formulations, details their contents and compares prices. Prescribers are also reminded that palatability can be an issue and that patients may need to try more than one formulation before finding a preference.

Product	Licensed Indication	Price (28 days)
Adcal –D3 (calcium 600mg/ vit D 400IU) Chewable tablets	**Adjunct in osteoporosis. 1 tablet twice daily**	**£4.06**
Adcal-D3 Dissolve (calcium 600mg/Vit D 400iu) Effervescent tablets	Adjunct in osteoporosis. 1 tablet twice daily	£4.99
Cacit D3 Effervescent granules (calcium 500mg/ Vit D 440IU)	Adjunct in osteoporosis. 1 or 2 sachets daily	£8.05
Calceos Chewable tabs (Calcium 500mg/ Vit D 400IU	**Adjunct in osteoporosis. 1 tablet twice daily**	**£3.59**
Calcichew D3 Forte Chewable tablets (calcium 500mg, Vit D 400IU)	**Adjunct in osteoporosis. 1 tablet twice daily**	**£4.20**
Calfovit D3 Sachets (calcium 1200mg/Vit D3 800IU)	**Adjunct in osteoporosis. 1 sachet daily**	**£4.04**

(Appropriate first line options are highlighted in bold)

PACEF Recommendations:
Prescribers should consider the use of calcium and vitamin D supplementation in all women receiving osteoporosis treatment where calcium intake and vitamin D stores are inadequate. Calcium and vitamin D supplementation should also be considered for the elderly in care homes at risk of fracture and in patients on long-term oral steroids with poor dietary intake. The role of calcium and vitamin D supplementation in the prevention of falls remains

unclear. Only calcium and vitamin D formulations containing an evidence based dose of each component should be prescribed (i.e. 1200mg of calcium and 800i.u. of vitamin D daily). Any of the preparations highlighted in bold in the table would be appropriate; all of the products highlighted are priced at approximately £4 per month. Cacit D3 effervescent sachets are expensive in comparison to competitors and should not be prescribed. Adcal D3 chewable tablets should be prescribed in preference to the more costly Adcal D3 Dissolve effervescent tablets. Calcichew D3 Forte chewable tablets are an appropriate first line choice, but Calcichew D3 chewable tablets should not be prescribed for these indications as they do not contain sufficient vitamin D3. Fosavance is a once weekly formulation of alendronate 70mg plus vitamin D3 2800IU priced comparably with branded once weekly Fosamax (alendronate) 70mg (£22.80 for 28 days' supply). This formulation contains insufficient vitamin D3, no calcium and is excessively priced in comparison to generic once weekly alendronate plus concurrent calcium and vitamin D. As a result of this, Fosavance is designated: RED-RED.

References

1. NICE Technology Appraisal 87, *Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women* (January 2005).
2. Chapuy M et al., *New Engl J Med* 1992; 327:1637-1642.
3. Avenell A et al., Vitamin D and vitamin D analogues for prevention of fractures associated with involutional and post-menopausal osteoporosis. *The Cochrane Database of Systematic Reviews* 2006, issue 4.
4. Porterhouse J et al., *BMJ* 2005; 330:1003 – 6.
5. NICE Clinical Guideline 21, *The assessment and prevention of falls in older people* (November 2004).
6. Bischoff-Ferrari HA et al., *JAMA* 2004; 291:1999-2006.
7. Royal College of Physicians, *Osteoporosis, clinical guidelines for prevention and treatment. Update on pharmacological interventions*. (Last updated 5 January 2001).
8. Bone & Tooth Society, National Osteoporosis Society, RCP, *Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London*, 2002

COZAAR-COMP TABLETS

Cozaar-Comp is a combination tablet containing losartan and hydrochlorothiazide licensed for the treatment of hypertension in patients not controlled on losartan or hydrochlorothiazide monotherapy. An additional strength of 100/12.5 (losartan 100mg/ hydrochlorothiazide 12.5mg) has just been licensed and joins two existing strengths already available: 100/25 and 50/12.5. The table below compares licensed indications and current prices for all available angiotensin II antagonists (A2As) including diuretic combinations. Prices for the two first line recommended Angiotensin Converting Enzyme Inhibitors (ACEIs), lisinopril and ramipril, are also included.

Product	Licensed Indication	Price (28's)
Cozaar-Comp tablets (Losartan plus hydrochlorothiazide)	Hypertension in patients whose BP is not controlled by hydrochlorothiazide or losartan monotherapy. Reduction in risk of stroke in hypertensive patients (except black patients) with left ventricular hypertrophy.	100mg/12.5mg £16.18 100mg/25mg £16.18 50mg/12.5mg £12.80

Losartan (Cozaar) tablets	Hypertension. Reductions in risk of stroke in hypertensive patients with left ventricular hypertrophy. Renal protection in type II diabetic patients with nephropathy.	25mg £16.18 50mg £12.80 100mg £16.18
Other A2As including diuretic combinations		
Candesartan (Amias) tablets	**Hypertension**	**4mg £8.15 , 8mg £9.89 16mg £12.72, 32mg £16.13**
Eprosartan (Teveten) tablets	Hypertension	300mg £11.63, 600mg £14.31
Irbesartan (Aprovel) tablets	Hypertension. Renal disease in hypertensive type II diabetes	75mg £10.29, 150mg £12.57 300mg £16.91
CoAprovel tablets (Irbesartan plus hydrochlorothiazide)	Hypertension in those inadequately controlled by either agent alone.	150mg/12.5mg £12.57 300mg/12.5mg £16.91 300mg/25mg £16.91
Olmesartan (Olmetec) tablets	**Hypertension**	**10mg £10.95, 20mg £12.95 40mg £17.50**
Olmetec Plus tablets (Olmesartan plus hydrochlorothiazide)	Hypertension in patients whose BP is not adequately controlled by olmesartan alone.	20mg/12.5mg £12.95 20mg/25mg £12.95
Telmisartan tablets (Micardis)	**Hypertension**	**20mg £9.25, 40mg £11.34 80mg £14.18**
Micardis Plus (Telmisartan plus hydrochlorothiazide)	Hypertension not adequately controlled by telmisartan alone.	40mg/12.5mg £11.34 80mg/12.5mg £14.18
Valsartan (Diovan) capsules	Hypertension	40mg £16.44, 80mg £16.44 160mg £21.66
Co-Diovan tablets Valsartan plus hydrochlorothiazide	Hypertension in patients whose BP is not controlled by valsartan or hydrochlorothiazide monotherapy.	80mg/12.5mg £16.44 160mg/12.5mg £21.66 160mg/25mg £21.66
Lisinopril tablets 2.5mg,5mg,10mg,20mg	**Hypertension**	**28 tabs £0.45-£1.32**
Ramipril capsules 1.25mg,2.5mg,5mg,10mg	**Hypertension**	**28 caps £0.65- £1.46**

PACEF Recommendation:

In the treatment of primary hypertension, A2As should be reserved for those patients who are intolerant to ACEIs. The incidence of cough associated with ACEI use is reported at being between 10 and 20% suggesting that 75 to 80% (or more) of renin angiotensin drug prescribing in practice should be for standard low cost generic ACEIs such as lisinopril or ramipril. Where an A2A is indicated, lower cost agents such as candesartan, olmesartan or telmisartan are advocated. Losartan has never been recommended for use in county, largely due to its high cost in comparison to alternative A2As. More recently, the price has fallen and it now more comparable with preferred agents. Neither losartan nor hydrochlorothiazide are preferred agents for the treatment of hypertension. As a result of this, Cozaar-Comp is designated: RED-RED

U-500 INSULIN (HUMULIN R)

Type 2 diabetes is a common condition characterised by insulin resistance and pancreatic failure. Many patients eventually require treatment with insulin and some, particularly the very obese, develop such severe insulin resistance that they require insulin in excess of 200 units per day for more than 48 hours. Other relatively rare disorders associated with severe insulin resistance include lipodystrophic diabetes and insulin receptor abnormalities. When patients require very large doses of insulin, each dose may have to be administered as two to three sequential injections or by re-dialling the insulin pen device several times. Such large volumes of injected insulin can be very uncomfortable and lead to problems with injection sites and poor concordance with treatment.

U-500 insulin is five times the strength of U-100 insulin and is available on a named patient basis as Humulin R from Eli Lilly & Co; it is imported into the UK from the USA by IDIS UK. There is evidence that U-500 insulin improves diabetic control, often at a lower daily dose than previously prescribed. Lower injected volumes and better glycaemic control help to improve patient satisfaction and concordance. There are currently only a small number of patients in county who are using U-500 insulin, but it is expected that this number will increase over time.

U500 insulin can only be initiated by a consultant diabetologist. Appropriate patients for initiation will typically require more than 200 units (often more than 300 units) of insulin daily and be experiencing injection site problems (due to multiple daily injections) and poor diabetic control despite large doses of insulin (HbA1c persistently above 8.5%). **All U-500 insulin is supplied by ULHT Pharmacy Department; patients normally receive three 20ml vials of U-500 insulin each time they order and order repeat prescriptions through their local diabetes centre. There is no requirement for GPs or primary care based dispensing or community pharmacy services to be involved.** The diabetes service is currently producing: a patient information leaflet; a U-500 insulin pathway and hospital safety guidelines covering the use of U-500 insulin.

PACEF Recommendation:
U-500 insulin should only be initiated by a consultant diabetologist; all repeat prescriptions and supplies should be accessed through the ULHT Diabetes Service and Pharmacy Department. U-500 insulin is designated: RED.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 136: STRUCTURAL NEUROIMAGING IN FIRST EPISODE PSYCHOSIS (FEBRUARY 2008)

The main recommendations are as follows:

- **Structural neuroimaging techniques** (either magnetic resonance imaging [MRI] or computed axial tomography [CT] scanning) are **not recommended** as a routine part of the initial investigations for the management of first-episode psychosis.

NICE TECHNOLOGY APPRAISAL 137: RITUXIMAB FOR THE TREATMENT OF RELAPSED OR REFRACTORY STAGE III OR IV FOLLICULAR NON-HODGKIN'S LYMPHOMA (FEBRUARY 2008)

The main recommendations are as follows:

- Rituximab (MabThera), within its marketing authorisation, in combination with chemotherapy, is **recommended** as an option for the **induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma.**
- Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is **recommended** as an option for the treatment of people with **relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab.**
- Rituximab monotherapy within its marketing authorisation, is **recommended** as an option for the treatment of people with **relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted** (i.e. if there is resistance to or intolerance of chemotherapy).

Rituximab (MabThera) is licensed:

- for relapsed or chemo-resistant stage III to IV follicular lymphoma.
- in combination with CVP chemotherapy for untreated stage III to IV follicular lymphoma.
- for maintenance therapy of relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera.
- in combination with CHOP chemotherapy for CD20 positive diffuse large B cell non-Hodgkin's lymphoma.

PACEF Recommendation:
Rituximab (MabThera) is designated RED for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma

NICE CLINICAL GUIDELINE 58: PROSTATE CANCER: DIAGNOSIS AND TREATMENT (FEBRUARY 2008)

The main recommendations are as follows:

Diagnosing prostate cancer

- **Before referral to specialist care, men with suspected prostate cancer should have been offered a prostate specific antigen level (PSA) and digital rectal examination (DRE) test.**
- To help the patient decide whether to have a prostate biopsy, healthcare professionals should discuss their PSA, DRE findings, the risks and benefits of biopsy, co-morbidities, risk factors (e.g. increasing age, black African/Caribbean ethnicity) and any previous history of negative prostate biopsy. The serum PSA alone should not lead to prostate biopsy.
- After a negative biopsy, the urological cancer specialist should review the man's risk (life expectancy, PSA level, DRE findings and estimated prostate size) and discuss risks/benefits of re-biopsy.

Before starting treatment

- Before starting treatment, patients, partners and carers should be informed of the effects of prostate cancer and that treatment may result in altered physical appearance, altered sexual experience, possible loss of sexual function, ejaculation and fertility and changes in urinary function.
- Before starting treatment, patients should be advised of the potential long-term adverse effects of treatment.
- All men with localised prostate cancer should be risk assessed according to risk stratification criteria: Low risk equates to a PSA < 10ng/ml **plus** a Gleason score ≤ 6 **and** a clinical stage of T1-T2a; Intermediate risk equates to a PSA 10-20ng/ml **or** a Gleason score of 7 **or** a clinical stage of T2b-T2c; High risk equates to a PSA >20ng/ml **or** a Gleason score of 8-10 **or** a clinical stage of T3-T4.

Localised prostate cancer

- **Treatment options for low risk localised prostate cancer include watchful waiting, active surveillance (preferred option), prostatectomy, brachytherapy and conformal radiotherapy.** Cryotherapy and high-intensity focused ultrasound are not recommended unless part of a clinical trial.
- **Treatment options for intermediate risk localised prostate cancer include watchful waiting, active surveillance, prostatectomy (preferred option), brachytherapy and conformal radiotherapy (preferred option).** Cryotherapy and high-intensity focused ultrasound are not recommended unless part of a clinical trial.
- **Treatment options for high risk localised prostate cancer include watchful waiting, prostatectomy (preferred option if there is a realistic prospect of long term disease control), and conformal radiotherapy (if there is a realistic prospect of long term disease control).** Active surveillance and brachytherapy are not recommended. Cryotherapy and high-intensity focused ultrasound are not recommended unless part of a clinical trial.

Localised prostate cancer: Radical treatments

- **Offer adjuvant hormonal therapy for a minimum of two years to men receiving radiotherapy who have a Gleason score of ≥ 8.**

Locally advanced prostate cancer

- **Offer neoadjuvant and concurrent luteinising hormone-releasing hormone agonist (LHRHa) therapy for 3 to 6 months to men receiving radiotherapy.**
- **Offer adjuvant hormonal therapy for a minimum of two years to men receiving radiotherapy who have a Gleason score of ≥ 8.**
- Consider pelvic radiotherapy for men with > 15% of pelvic lymph node involvement who are to receive neoadjuvant hormonal therapy and radiotherapy.
- **Do not offer: adjuvant hormonal therapy in addition to prostatectomy, bisphosphonates to prevent bone metastases, immediate post-operative radiotherapy routinely after prostatectomy or cryotherapy or high-intensity focused ultrasound unless part of a clinical trial.**

Metastatic prostate cancer

- Offer bilateral orchidectomy as an alternative to continuous LHRHa therapy.

- **Offer monotherapy with bicalutamide (150mg) if the man hopes to retain sexual function and is willing to accept gynaecomastia and reduced survival.**
- **Offer androgen withdrawal in place of bicalutamide, if bicalutamide is not successful in retaining sexual function. Regular resistance exercise reduces fatigue and improves quality of life.**
- **Consider intermittent androgen blockade (inform the patient of lack of long-term term evidence of effectiveness).**
- **Do not offer combined androgen blockade as a first-line treatment.**

Hormone-refractory prostate cancer

- **Offer docetaxel only if Karnofsky score is ≥ 60%.** Stop treatment after 10 planned cycles or if severe adverse events occur or if disease progresses. Do not repeat treatment cycles if disease recurs.
- **Offer a corticosteroid (e.g. dexamethasone 0.5mg daily) as a third–line therapy after androgen withdrawal and anti-androgen therapy.**
- Offer spinal MRI if spinal metastases are found and spine related symptoms develop.
- Offer decompression of the urinary tract by percutaneous nephrostomy or insertion of a double J stent to men with obstructive uropathy.
- **Do not offer routine spinal MRI to men with known bone metastases or bisphosphonates to prevent or reduce complications of bone metastases.**

Follow up

- Check PSA levels of men who are having radical treatment at least 6 weeks after treatment and at least every 6 months for the first two years and at least once a year after the first 2 years.

Managing side effects of treatment

- Early and ongoing access to specialist erectile dysfunction services and specialist psychosexual services should be available. **Offer phosphodiesterase type 5 inhibitors to men who experience erectile dysfunction. Where contra-indicated or insufficiently effective offer vacuum devices, intraurethral inserts, penile injections or prostheses.**
- Specialist continence services should be available for assessment, diagnosis and treatment of troublesome urinary symptoms (e.g. coping strategies, pelvic floor muscle re-education, bladder retraining and pharmacotherapy).
- Men with intractable stress incontinence should be referred to a specialist surgeon and considered for an artificial urinary sphincter.
- Urological assessment should be available if troublesome urinary symptoms are present.

Side effects of hormonal treatments

- Offer oral or parenteral synthetic progestogens first line for hot flushes. Offer oral therapy for 2 weeks and re-start when flushes recur, if effective (e.g. megestrol acetate)
- Offer prophylactic orthovoltage or electron beam radiotherapy to breast buds (single 8 Gy fraction) within the first month of long-term (>6months) treatment with bicalutamide monotherapy.
- Consider weekly tamoxifen if radiotherapy does not prevent gynaecomastia.
- Do not routinely offer bisphosphonates to prevent osteoporosis in men receiving androgen withdrawal therapy.

Much more detailed guidance and accompanying treatment algorithms are included in the full text of the NICE Clinical Guideline. For further information visit the NICE website: www.nice.org.uk

MHRA SAFETY UPDATE: KETOCONAZOLE AND MODAFINIL

The *Medicines and Healthcare products Regulatory Agency (MHRA) Safety Update* featured ketoconazole and modafinil in its March 2008 edition. Full details are available from http://www.mhra.gov.uk/mhra/drugsafetyupdate

KETOCONAZOLE

Ketoconazole (Nizoral) is an imidazole antifungal agent which is indicated for the treatment of skin, hair and mucosal mycoses that cannot be treated with other antifungals. It is better absorbed by mouth than other imidazoles.
The use of ketoconazole has been associated with fatal hepatotoxicity and the Committee on the Safety of Medicines (CSM) has previously warned that prescribers should weigh the potential benefits of ketoconazole treatment against the risk of liver damage and should carefully monitor patients both clinically and biochemically. Ketoconazole should not be used orally for the treatment of superficial fungal infections. After a further review of the risks of serious hepatotoxicity, the range of approved therapeutic indications has been reduced to:

- Treatment of dermatophytosis and Malassezia folliculitis that cannot be treated topically because of the site, extent of the lesion, or deep infection of the skin resistant to, or in patients intolerant of, fluconazole, terbinafine and itraconazole.
- Treatment of chronic mucocutaneous candidosis, cutaneous candidosis and oropharyngeal candidosis that cannot be treated topically because of the site, extent of the lesion, or deep infection of the skin resistance to, or in patients intolerant of, both fluconazole and itraconazole.

Healthcare professionals are advised that:

- Ketoconazole tablets are not suitable as first-line treatment or for superficial infections
- Ketoconazole tablets should be initiated by a physician who is experienced in the management of fungal infections
- Ketoconazole should only be used when potential benefits are considered to outweigh potential risks, taking into consideration the availability of other effective antifungal therapy
- The risk of serious hepatotoxicity increases with duration of treatment. It is recommended that ketoconazole therapy should not be continued beyond 10 days, unless full consideration has been give to the extent of the response to treatment and an evaluation of the risks and benefits of continuing had been undertaken.
- Liver function must be monitored before starting treatment, at week 2, at week 4 and then monthly.

PACEF Recommendation:
Having reviewed MHRA advice on ketoconazole, PACEF have designated oral ketoconazole as RED. Treatment should be initiated by a physician experienced in the management of fungal infections; in the majority of cases it

would be reasonable to expect the full course to be provided and monitored from secondary or tertiary care. Ketoconazole is not currently on the ULHT Hospital Formulary and so is unlikely to be initiated from within Lincolnshire Hospitals.

MODAFINIL (PROVIGIL)

Modafinil (Provigil) is a 'black triangle' drug licensed for the symptomatic relief of excessive sleepiness associated with narcolepsy, obstructive sleep apnoea/ hypopnoea syndrome and moderate to severe chronic shift work sleep disorder. **The use of modafinil has been associated with serious skin reactions such as Stevens Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis.** These conditions usually occur within the first five weeks of treatment, although cases have been reported after more than 3 months treatment. **There have also been reports of suicidal ideation, hallucinations, delusion, aggression, psychosis and mania.** These reactions have occurred mainly in patients with a history of mental illness.

Healthcare professionals are advised that:

- Modafinil should be discontinued at the first sign of a rash and not restarted.
- Modafinil should be discontinued in patients who experience any psychiatric symptoms and not restarted.
- Modafinil should be used with caution in patients with a history of psychosis, depression or mania
- Modafinil should be used with caution in patients with a history of alcohol, drug or illicit substance abuse.

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7th May 2008