NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 2; Number 19 **December 2008**

HAPPY CHRISTMAS TO ALL OUR READERS

What's new this month:

- **Dexibuprofen and dexketoprofen, isomers of ibuprofen and ketoprofen, are assessed (see pages 3 and 4).**
- **The JUPITER Study compares rosuvastatin with placebo in a primary prevention population and is assessed (see page 4).**
- **Two new shared care guidelines are launched (see page 6).**
- **Clostridium difficile is reviewed (see page 6).**
- **New NICE guidance on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal osteoporosis is reviewed (see pages 7 to 10).**
- **The new NICE Clinical Guideline on familial hypercholesterolaemia 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. Steps will be taken to ensure the widest possible distribution across NHS Lincolnshire 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: DECEMBER UPDATE

Drug	Indication(s)	Traffic Light Status
Alendronate 70mg tabs (generic)	Treatment of postmenopausal osteoporosis.	GREEN First line bisphosphonate of choice in both the primary and secondary prevention of postmenopausal osteoporosis (subject to NICE criteria)

Clopidogrel tablets 300mg (Plavix)	For use as a loading dose in patients with non-ST segment elevation acute coronary syndrome (i.e. unstable angina or non-Q-wave myocardial infarction (MI)) and ST segment elevation acute MI.	RED
Dexibuprofen tablets 300mg and 400mg (Seractil)	Osteoarthritis, dysmenorrhoea, mild to moderate pain and dental pain.	RED-RED
Dexketoprofen tablets 25mg (Keral)	Musculoskeletal pain, dysmenorrhoea, dental pain	RED-RED
Disodium etidronate (Didronel PMO)	Treatment of osteoporosis; prevention of bone loss in post menopausal women	GREEN Second line alternative bisphosphonate in patients who are unable to take, intolerant or contra-indicated to alendronate in both the primary and secondary prevention of postmenopausal osteoporosis (subject to NICE criteria).
Raloxifene (Evista) 60mg tablets	Treatment and prevention of postmenopausal osteoporosis	RED-RED for the primary prevention of postmenopausal osteoporosis GREEN Third line alternative in patients who are unable to take, intolerant or contra-indicated to alendronate and either risedronate or etidronate in both the secondary prevention of postmenopausal osteoporosis (subject to NICE criteria).
Risedronate 35mg tabs (Actonel Once a Week)	Treatment of postmenopausal osteoporosis.	GREEN Second line alternative bisphosphonate in patients who are unable to take, intolerant or contra-indicated to alendronate in both the primary and secondary prevention of postmenopausal osteoporosis (subject to NICE criteria).
Strontium ranelate (Protelos) 2g sachet	Treatment of postmenopausal osteoporosis to reduce risk of vertebral and hip fractures	GREEN Third line alternative in patients who are unable to take, intolerant or contra-indicated to alendronate and either risedronate or etidronate in both the primary and secondary prevention of postmenopausal osteoporosis (subject to NICE criteria).
Teriparatide (Forsteo) injection 250mcg per ml, 3ml pre-filled syringe	Treatment of osteoporosis in postmenopausal women	RED-RED for the primary prevention of postmenopausal osteoporosis RED for fourth line use in patients who are unable to take, intolerant or contra-indicated to alendronate and either risedronate or etidronate and strontium ranelate or raloxifene in the secondary prevention of postmenopausal osteoporosis (subject to NICE criteria).

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 LPFT **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.

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 ASSESSMENTS

RAPID ASSESSMENT: DEXIBUPROFEN TABLETS (SERACTIL)

Dexibuprofen (Seractil) is the active S (+) isomer of racemic ibuprofen. It is formulated in 300mg and 400mg tablets and licensed for osteoarthritis, dysmenorrhoea, mild to moderate pain and dental pain. The usual dose is 400mg twice daily up to a maximum of 400mg three times daily. Review of the trial data uncovered no strong evidence to suggest dexibuprofen is superior to generic ibuprofen in terms of clinical efficacy, although it may have a slightly quicker onset of action. A meta analysis of five short-term studies has suggested that dexibuprofen has a lower incidence of adverse events than ibuprofen, although none of the trials included in the meta-analysis lasted for longer than 21 days. Due to the short-term nature of these studies, this cannot be considered as conclusive evidence of improved tolerability. In addition, treatment with dexibuprofen costs 3-4 times more than generic ibuprofen preparations:

Drug	Dose	28 days supply
Ibuprofen tablets 400mg (generic)	400mg three times daily	£2.31
Dexibuprofen tablets 400mg	400mg twice daily	£9.31
Dexibuprofen tablets 400mg	400mg three times daily	£13.96

PACEF Recommendation:
The recent NICE Clinical Guideline on osteoarthritis (OA) (see *PACE Bulletin*, Vol 2, No 7 (May 2008)) recommends low dose ibuprofen as the first line oral non-steroidal anti-inflammatory drug (NSAID) of choice in the treatment of OA and makes no reference to isomer preparations. The evidence base to support the use of dexibuprofen as an alternative to ibuprofen is inadequate; claims of better tolerability are based on short-term studies and, at best, this isomer is equivalent, but not superior, to ibuprofen in terms of clinical efficacy. It is also prohibitively expensive. As a result of this, dexibuprofen (Seractil) is designated RED-RED.

RAPID ASSESSMENT: DEXKETOPROFEN TABLETS (KERAL)

Dexketoprofen is the active isomer of ketoprofen and is marketed as 25mg tablets under the brand name of Keral. It is licensed for the treatment of mild to moderate pain, such as musculo-skeletal pain, dysmenorrhoea and dental pain. Clinical trials have shown similar analgesic efficacy to ketoprofen and ibuprofen. The manufacturer claims a faster onset of action, although this is not seen at all doses and there is no significant difference in time to maximal pain relief between dexketoprofen and ketoprofen (2.6 and 3.0 hours). The original clinical trials for this product were published in a journal supplement and may never have been subject to peer review. There is no evidence that dexketoprofen is any better tolerated than ketoprofen; the MHRA have previously raised concerns about the risk of serious gastrointestinal side effects associated with ketoprofen. In addition, treatment with dexketoprofen costs significantly more than generic ibuprofen preparations:

Drug	Dose	28 days supply
Ibuprofen tablets 400mg (generic)	400mg three times daily	£2.31
Ketoprofen capsules 50mg (generic)	50mg twice daily	£18.64
Ketoprofen capsules 100mg (generic)	100mg twice daily	£6.66
Dexketoprofen tablets 25mg (Keral)	25mg three times daily (maximum daily dose)	£15.42

(Prices quoted are from the *Drug Tariff*, December 2008 and MIMS, December 2008)

PACEF Recommendation:
The evidence base to support the use of dexketoprofen in any context is inadequate. Continuing concerns over the risk of serious gastrointestinal effects with ketoprofen are also applicable to this isomer. As a result of this dexketoprofen (Keral) is designated: RED-RED.

RAPID ASSESSMENT: CLOPIDOGREL TABLETS 300MG (PLAVIX)

The 300mg tablet of clopidogrel (Plavix) is intended for use as a loading dose in patients with non-ST segment elevation acute coronary syndrome (i.e. unstable angina or non-Q-wave myocardial infarction (MI)) and ST segment elevation acute MI. A single loading dose of 300mg is indicated initially followed by a daily maintenance dose of 75mg.

PACEF Recommendation:
Clopidogrel 300mg tablets (Plavix) are approved for use solely in secondary care within licensed indications. Prescribers are reminded that 300mg is a loading dose; all patients discharged from hospital on clopidogrel should already be established on the 75mg daily maintenance dose. As a result of this clopidogrel 300mg tablets are designated as RED.

NEW TRIAL ASSESSMENT: THE JUPITER STUDY

On publication in November, the JUPITER study (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) caused something of a stir in both the popular and medical press. In this randomised controlled trial, 17,802 healthy men and women (median age 66 years) with low-density lipoprotein cholesterol (LDL-C) levels of less than 3.4 mmol/L and high sensitivity C-reactive protein (hs-CRP) levels greater than or equal to 2.0 mg/L were randomised either to rosuvastatin 20mg once daily or placebo. The combined primary end point included MI, stroke, arterial revascularisation, hospitalisation for unstable angina and death from cardiovascular causes. The median follow up time was 1.9 years (with a maximum of 5 years).

Hs-CRP is an inflammatory biomarker that independently predicts future vascular events and improves global classification of risk, regardless of the LDL cholesterol level; other statins (e.g. pravastatin) have previously been shown to reduce hs-CRP.

JUPITER was designed to have the statistical power to detect a 25% reduction in the rate of the primary end point, but, in order to achieve this significance level, 520 primary events had to have occurred. The study was stopped early when the monitoring board noted a significant reduction in events in those assigned to active treatment, however at that stage only 393 primary events had occurred. This probably exaggerated the results to some degree.

In the rosuvastatin group, there were 142 primary events compared to 251 events in the placebo group. These figures and the calculated Absolute Risk Reduction (ARR) and number needed to treat (NNT) are tabulated below:

Rosuvastatin	Placebo
142 / 8901	251 / 8901
= 1.59%	=2.82%

Absolute risk reduction = 2.82 – 1.59 = 1.23%

Numbers needed to treat (NNT) = 100 / 1.23 = 81 for 1.9 years

Cost to prevent one primary event = £26.02 x 13 x 81 x 1.9 = £52,058

Of concern is the significantly higher incidence of physician-reported diabetes in the rosuvastatin group (3.0% vs. 2.4% in the placebo group; p=0.01, RR 1.25, NNH 165). The median HbA1c values differed very slightly, but significantly (5.9% vs 5.8%; p=0.001). There is also no long-term safety data on lowering LDL cholesterol to 1.4mmol/L, the median value achieved in this study.

The absolute benefits and harms are that for every 1000 people who took rosuvastatin 20mg daily for 2 years, 8 people avoided having an MI or stroke or dying from CV causes, but 6 people developed diabetes who would not have done so otherwise.

This study provides further evidence of the effectiveness of statin therapy in reducing cardiovascular risk within a primary prevention context. It is also the first study reporting improvements in patient outcomes associated with rosuvastatin. It confirms the findings of other studies that have shown that reducing LDL-C levels reduces the incidence of cardiovascular and cerebrovascular events. The NICE Clinical Guideline on Lipid Modification recommends that treatment for the primary prevention of CVD should be offered to patients with a 10 year risk of CVD of ≥ 20%. The placebo arm of the JUPITER trial was comprised of study participants with a roughly 9 – 15% 10 year risk of cardiovascular disease. This confirms what is already known (i.e. that the primary prevention threshold is arbitrary and that treating patients below this threshold is likely to prevent further events). What remains to be evaluated is the cost-effectiveness of pursuing such a strategy within primary care.

In summary, following review of JUPITER, a number of concerns remain:

(1) The cost-effectiveness of lowering the primary prevention threshold below 20% 10 year risk of CVD has not yet been evaluated. The high cost of rosuvastatin is unlikely to render it cost-effective within the primary prevention context.
(2) JUPITER is a placebo controlled trial; comparative data against simvastatin 40mg within a primary prevention context would have been more useful.
(3) The validity of the JUPITER results was compromised by the decision to terminate the study before results achieved full significance.

(4) The higher incidence of diabetes in the rosuvastatin arm of the study requires further investigation.
(5) The MHRA have specifically cautioned against the initiation of rosuvastatin at a dose of 20mg.

PACEF Recommendation:
Prescribers should continue to follow national policy on the use of statins in the primary prevention of CVD. Specifically: (1) Utilize a systematic strategy to identify people aged 40 to 74 who are likely to be at high risk; (2) Use a primary prevention threshold of 20% or greater 10-year risk of developing CVD; (3) Initiate treatment with simvastatin 40mg unless potential drug interactions, contraindication or poor tolerability necessitate the use of a lower dose or pravastatin; (4) Do not treat to target; target chasing is inappropriate in primary prevention; and (5) Do not use atorvastatin, rosuvastatin, omega 3 fatty acid supplements (such as Omacor and Maxepa), fibrates, nicotinic acid or anion exchange resins for primary prevention. Ezetimibe should only be used within licensed indications (i.e. primary hypercholesterolaemia).

Reference
'Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein' *N Engl J Med* 2008; 359:2195 – 2207.

SHARED CARE GUIDELINES

PACEF have approved two shared care guidelines this month. These are:

- Nabilone in the management of chronic neuropathic pain
- Erythropoiesis Stimulating Agents in the treatment of Anaemia of Chronic Kidney Disease

Copies are available from Cathy Johnson, Interface Lead Pharmacist at cathy.johnson@lpct.nhs.uk

UPDATE ON *CLOSTRIDIUM DIFFICILE*

Despite our best efforts, the incidence of Clostridium difficile originating in primary care continues to be a problem. A series of Q&As published recently by the UK Medicines Information Service provides helpful background information:

- *Clostridium difficile* (*C. diff*) infection is a leading cause of iatrogenic outbreaks of diarrhoea and increases mortality and healthcare costs. Patients most at risk of *C.diff* infection are the elderly, immunosuppressed and debilitated.
- Previous antimicrobial use is a major risk factor for *C.diff* associated disease (CDAD). Antimicrobials disrupt the normal microflora of the colon and allow colonisation of the pathogen.
- Broad-spectrum antimicrobials are most strongly implicated in CDAD, particularly third generation cephalosporins, aminopenicillins and quinolones. The use of broad spectrum antimicrobials should be avoided, especially in patients with risk factors for *C.diff* infection.
- The risk of CDAD is increased by long or repeated courses and use of multiple antimicrobials.
- *C.diff* infection is treated with oral metronidazole or vancomycin.
- Available studies do not provide sufficient evidence to support the routine use of probiotics for the prevention or treatment of *C.diff* infection.
- The use of proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs), which suppress gastric acid secretion, has also been suggested as a risk factor for the development of CDAD. Observational case-control and cohort studies undertaken to explore this association have produced conflicting results and have failed to establish a causal link. If there is an association, it is probably stronger for PPIs than H2RAs. It would seem prudent to restrict PPI use wherever possible.

NICE TECHNOLOGY APPRAISAL 160: *ALENDRONATE, ETIDRONATE, RISEDRONATE, RALOXIFENE AND STRONTIUM RANELATE FOR THE PRIMARY PREVENTION OF OSTEOPOROTIC FRAGILITY FRACTURES IN POSTMENOPAUSAL WOMEN* (OCTOBER 2008)

This TA relates only to treatments for the primary prevention of fragility fractures in postmenopausal women who have osteoporosis. Osteoporosis is defined by a T-score of -2.5 standard deviations (SD) or below on dual-energy X-ray absorptiometry (DXA) scanning. However, the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible.

The key recommendations from this TA are summarized in the following algorithm:

Women aged ≥ 70 yrs with an **independent clinical risk factor for fracture**[1] or an **indicator of low BMD**[2] and **confirmed osteoporosis** (women aged ≥ 75 yrs with 2 or more independent clinical risk factors[1] or indicators of low BMD[2] may not require a DXA scan)

Women aged 65-69 with an **independent clinical risk factor for fracture**[1] and **confirmed osteoporosis** (T score ≤ -2.5SD)

Postmenopausal women younger than 65 with an **independent clinical risk factor**[1] and **at least one additional indicator of low BMD**[2] and **confirmed osteoporosis** (T score ≤ -2.5SD)

Alendronate once-weekly tabs 70mg (generic)

Intolerance[3] of or contraindication to alendronate

Risedronate or etidronate but only if these criteria are met:

T-scores (SD) at (or below) which risedronate or etidronate is recommended when alendronate cannot be taken

Number of independent clinical risk factors[1] for fracture

Age (years)	0	1	2
65-69	a	-3.5	-3.0
70-74	-3.5	-3.0	-2.5
75 or older	-3.0	-3.0	-2.5

[a] Treatment with risedronate or etidronate is not recommended.

Intolerance[3] of or contraindication to alendronate and either risedronate or etidronate

Strontium ranelate but only if these criteria are met:

T-scores (SD) at (or below) which strontium ranelate is recommended when alendronate and either risedronate or etidronate cannot be taken

Number of independent clinical risk factors[1] for fracture

Age (years)	0	1	2
65-69	a	-4.5	-4.0
70-74	-4.5	-4.0	-3.5
75 or older	-4.0	-4.0	-3.0

[a] Treatment with strontium ranelate is not recommended.

[1] **Independent clinical risk factors for fracture** are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

[2] **Indicators of low BMD** are low BMI (<22kg/m^2), medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause

[3] Defined as inability to comply with the special instructions for administration or persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.

Additional notes:

- This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and/or vitamin D supplementation should be considered (calcium 1200mg + vitamin D_3 800 units daily recommended locally). Calcium and vitamin D supplementation was last reviewed in *PACE Bulletin* Vol 2, No 6 (May 2008); preferred supplements are: Adcal D3 chewable tablets, Calceos chewable tablets and Calcichew D3 Forte chewable tablets.
- A NICE Clinical Guideline entitled *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk* is due shortly.
- Separate guidance is in process to cover the role of these drugs in the primary prevention of osteoporotic fragility fractures in women on long term systemic steroid therapy.
- Prescribers are reminded that the combined effects of strontium distribution in bone and increased X-ray absorption of strontium as compared to calcium, leads to an amplification of bone mineral density (BMD) measurement by DXA scanning. Available data indicate that these factors account for approximately 50% of the measured change in BMD over 3 years of treatment with strontium 2 g/day. This should be taken into account when interpreting BMD changes during treatment. Although strontium therapy does not prohibit the use of future DXA scans to monitor the progress of the disease, it appears to produce a falsely high reading of BMD which will render any future comparison to baseline invalid.

Cost comparison

Product	**Licensed Indication and Recommended Dosage**	**Cost of 28 Days Treatment**
Alendronate 70mg tabs	**Treatment of postmenopausal osteoporosis. One tablet a week.**	**£1.82**
Disodium etidronate (Didronel PMO)	Treatment of osteoporosis; prevention of bone loss in post menopausal women Taken in 90 day cycles: 1 Didronel tablet for 14 days followed by 1 calcium carbonate 1.25g tablet (Cacit) for 76 days	£6.57
Risedronate 35mg tabs (Actonel Once a Week)	Treatment of postmenopausal osteoporosis. One tablet a week.	£20.30
Raloxifene (Evista) 60mg tablets	Treatment and prevention of postmenopausal osteoporosis 60mg once daily	£17.06
Strontium ranelate (Protelos) 2g sachet	Treatment of postmenopausal osteoporosis to reduce risk of vertebral and hip fractures 2g once daily	£25.60

(Prices quoted are from the *Drug Tariff*, December 2008 and MIMS, December 2008)

NICE TECHNOLOGY APPRAISAL 161: *ALENDRONATE, ETIDRONATE, RISEDRONATE, RALOXIFENE, STRONTIUM RANELATE AND TERIPARATIDE FOR THE SECONDARY PREVENTION OF OSTEOPOROTIC FRAGILITY FRACTURES IN POSTMENOPAUSAL WOMEN* (OCTOBER 2008)

This TA relates only to treatments for the secondary prevention of fragility fractures in postmenopausal women who have osteoporosis and have sustained a clinically apparent osteoporotic fragility fracture. Osteoporosis is defined by a T-score of -2.5 standard deviations (SD) or lower on DXA scanning. However, the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible.

Alendronate once-weekly tabs 70mg (generic)

↓

Intolerance[1] of or contraindication to alendronate

↓

Risedronate or etidronate but only if these criteria are met:

T-scores (SD) at (or below) which risedronate or etidronate is recommended when alendronate cannot be taken

	Number of independent clinical risk factors for fracture [2]		
Age (years)	0	1	2
50-54	a	-3.0	-2.5
55-59	-3.0	-3.0	-2.5
60-64	-3.0	-3.0	-2.5
65-69	-3.0	-2.5	-2.5
70 or older	-2.5	-2.5	-2.5

[a] Treatment with risedronate or etidronate is not recommended.

↓

Intolerance[1] of or a contraindication to alendronate and either risedronate or etidronate

↓

Strontium ranelate or raloxifene but only if these criteria are met:

T-scores (SD) at (or below) which strontium ranelate or raloxifene is recommended when alendronate and either risedronate or etidronate cannot be taken

	Number of independent clinical risk factors for fracture*		
Age (years)	0	1	2
50-54	a	-3.5	-3.5
55-59	-4.0	-3.5	-3.5
60-64	-4.0	-3.5	-3.5
65-69	-4.0	-3.5	-3.0
70-74	-3.0	-3.0	-2.5
75 or older	-3.0	-2.5	-2.5

[a] Treatment with strontium or raloxifene is not recommended.

[1] Unable to comply with the special instructions for administration or persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.

[2] Independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

Intolerance of strontium ranelate is defined as persistent nausea or diarrhoea, either of which warrants discontinuation of treatment.

Additional notes:

- An unsatisfactory response is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below her pre-treatment baseline.
- This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and/or vitamin D supplementation should be considered (calcium 1200mg + vitamin D_3 800 units daily recommended locally). Calcium and vitamin D supplementation was last reviewed in *PACE Bulletin* Vol 2, No 6 (May 2008).
- **Teriparatide (Forsteo)** is recommended as an alternative for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: (1) who are unable to take alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate or who have a contra-indication to or are are intolerant of strontium ranelate (see below) or who have had an unsatisfactory response to treatment with alendronate, residronate or etidronate and; (2) who are 65 or older and have a T-score of -4.0 SD or below, or a T-score of – 3.5 SD or below plus more than two fractures or who are aged 55-64 and have a T-score of -4 SD or below plus more than two fractures.
- The Scottish Medicines Consortium have recommended that teriparatide should be initiated by specialists experienced in the treatment of osteoporosis.
- Teriparatide is a subcutaneous injection. Patients are trained to self-administer. A single 18 month course is advocated which should not be repeated in the patient's lifetime. The injection requires storage in a refrigerator both before and after the pre-filled pen is started. Once started the contents of the pen are stable in the refrigerator for 28 days.

Cost

Product	Licensed Indication and Recommended Dosage	Cost of 28 Days Treatment
Teriparatide (Forsteo) injection 250mcg per ml, 3ml pre-filled syringe	Treatment of osteoporosis in postmenopausal women 20mcg daily by SC injection	£271.88

(Prices quoted are from MIMS, December 2008)

PACEF Recommendations:
Prescribers are asked to utilize the relevant algorithm when prescribing bisphosphonates or any other bone-sparing agent in the primary or secondary prevention of osteoporotic fracture in postmenopausal osteoporosis. Generic alendronate 70mg once weekly should always be considered first line unless contra-indicated. The low cost of generic alendronate in comparison to premium price branded equivalents has resulted in the NICE cost model concluding that some patients that are cost-effective to treat with alendronate first line are not cost effective to continue to treat if a second line choice becomes necessary due to intolerance or contra-indication. The relevant tables in each algorithm can help to determine the most cost-effective treatment option at each stage. Prescribers are reminded of the importance of adequate calcium and vitamin D intake or calcium and vitamin D supplementation in these patients. The Traffic Light designations of each of these drugs are summarized at the front of this issue of the bulletin.

NICE CLINICAL GUIDELINE 71: *FAMILIAL HYPERCHOLESTEROLAEMIA – IDENTIFICATION AND MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLAEMIA* (AUGUST 2008)

The key recommendations are as follows:

Diagnosis

- Consider the possibility of familial hypercholesterolaemia (FH) in adults who have a raised total cholesterol (TC) concentration (typically greater than 7.5mmol/l), especially if there is a personal or family history of premature CHD.
- Exclude secondary causes before making the FH diagnosis.
- Use the Simon Broome diagnostic criteria to make the diagnosis of FH:

Simon Broome diagnostic criteria

- Diagnose definite FH in adults if TC and LDL-C concentrations are above 7.5mmol/l and 4.9mmol/l respectively with tendon xanthomas or evidence of these signs in first or second degree relatives. In a child or young person, the TC and LDL-C concentrations are above 6.7mmol/l and 4.0mmol/l respectively with tendon xanthomas or evidence of these signs in first or second degree relatives.
- Alternatively definite FH can be diagnosed from DNA based evidence of an LDL-receptor mutation, familial defective apo B-100 or a PCSK9 mutation.
- Diagnose possible FH if TC and LDL-C concentrations are as defined above and the patient has at least one of the following risk factors: (1) Family history of myocardial infarction aged younger than 50 years in a second-degree relative or younger than 60 years in a first degree relative; (2) Family history of raised TC (>7.5mmol/l) in adult first or second degree relative or > 6.7mmol/l in child, brother or sister aged younger than 16.

- The absence of clinical signs (e.g.tendon xanthoma) does not exclude a diagnosis of FH.
- To confirm a diagnosis take two measurements of LDL-C concentrations.
- In children at risk of FH because of one affected parent, offer a DNA test if the family mutation is known (before the child is 10 or as soon as possible thereafter); if the family mutation is not known, measure LDL-C
- In children at risk of FH because of two affected parents or the presence of clinical signs (e.g. cutaneous lipid deposits), measure LDL-C before the age of 5; if LDL-C is greater than 11mmol/l consider a clinical diagnosis of homozygous FH.
- Always take a family history of premature CHD including, when possible, a three generation pedigree (including relatives' age of onset of CHD (or age and cause of death), lipid concentrations, smoking history).
- Consider a clinical diagnosis of homozygous FH in adults with an LDL-C concentration greater than 13mmol/l or children/young people with an LDL-C greater than 11mmol/l.
- Offer all people with a clinical diagnosis of homozygous FH a referral to a specialist centre; consider referral to a cardiologist for evaluation of CHD.
- Offer a DNA test to people with a clinical diagnosis of FH.
- Do not use ultrasonography of the Achilles tendon.
- Do not use CHD risk estimation tools; people with FH are already at high risk of premature CHD.

Information for women and girls with FH

- Discuss the risks of lipid modifying therapy on future pregnancy and the risks to the fetus.
- Consider alternatives to the combined oral contraceptive as there is a small increased risk of CV events.
- Women planning to conceive should not take lipid modifying therapy; women should be advised to stop lipid modifying therapy 3 months before attempting to conceive.
- If conception occurs while a women is taking lipid modifying therapy, advise immediate cessation of treatment.
- Do not routinely measure TC/LDL-C during pregnancy.
- Do not use any lipid modifying therapy (except bile acid sequestrants) during breast feeding.

Lifestyle advice

- Standard advice relating to smoking, diet, physical activity, weight management and alcohol consumption applies.
- Do not routinely recommend omega-3 fatty acid supplements (e.g. Omacor, Maxepa).

Management

- Use statins first line and aim to achieve at least 50% reduction of LDL-C concentration from baseline. High-intensity statins are recommended, increased to the maximum licensed or tolerated dose. NICE define 'higher intensity statins' as those used in doses that produce greater cholesterol lowering than simvastatin 40mg, for example simvastatin 80mg. The comparative table below compares LDL-C reduction figures for each of the major statins at each dose:

Percentage Reductions in LDL Cholesterol and Total Cholesterol

Higher intensity statins are highlighted in bold

Statin	Daily Dose	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol
Atorvastatin	10mg	£18.03	37%	32%
Atorvastatin	**20mg**	**£24.64**	**43%**	**36%**
Atorvastatin	**40mg**	**£28.21**	**49%**	**42%**
Atorvastatin	**80mg**	**£28.21**	**55%**	**47%**
Pravastatin	40mg	£2.77	29%	29%
Rosuvastatin	**5mg**	**£18.03**	**38%**	**33%**
Rosuvastatin	**10mg**	**£18.03**	**43%**	**37%**
Rosuvastatin	**20mg**	**£26.02**	**48%**	**40%**
Simvastatin	40mg	£1.37	37%	31%
Simvastatin	**80mg**	**£2.94**	**42%**	**35%**

(Prices quoted are from the *Drug Tariff*, December 2008)

- Choose the statin licensed for use in the appropriate age group. Guidance on the use of atorvastatin, pravastatin and simvastatin in children is given in the *BNF for children*. Prescribe the doses specified.
- Ezetimibe is an option for adults with heterozygous FH if statins are contraindicated or not tolerated.
- Combination statin/ezetimibe therapy is an option for adults with heterozygous FH if TC or LDL-C concentrations are not appropriately controlled with statins alone.

PACEF Recommendations

Simvastatin 40mg to 80mg should be used first line with an aim to achieve at least 50% reduction of LDL-C concentration from baseline. Such an ambitious target LDL-C reduction may necessitate use of alternative high-intensity statins increased to their maximum licensed or tolerated doses. Atorvastatin 40mg to 80mg or rosuvastatin 20mg to 40mg may be indicated. Prescribers are reminded of the risk of dose-related side effects; specifically, there is an increased incidence of myopathy if a statin is given at a high dose or given in combination with a fibrate or nicotinic acid. Where one statin is not tolerated, an alternative statin should be tried before ezetimibe monotherapy is considered. This is because ezetimibe monotherapy is not as effective in terms of TC and LDL-C lowering as even a low dose of simvastatin; ezetimibe is also a black triangle drug.

If ezetimibe/statin combination therapy becomes necessary due to intolerance or inadequate response, an ezetimibe/simvastatin combination should be preferred. Co-prescribing of high-cost, high-potency statins with ezetimibe is prohibitively expensive and should be reserved for exceptional circumstances. Where exceptionally high TC or LDL-C

reductions are required, a combination of ezetimibe and simvastatin 80mg should be considered. A fixed dose combination formulation of ezetimibe and simvastatin (Inegy) is available in a variety of strengths, but is significantly more expensive than separate components and should not be prescribed.

Percentage Reductions in LDL Cholesterol and Total Cholesterol: Ezetimibe and Inegy

Drug	Daily Dose	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol
Simvastatin	40mg	£1.37	37%	31%
Simvastatin	80mg	£2.94	42%	35%
Ezetimibe	**10mg**	**£26.21**	**17-19%**	**12-13%**
Ezetimibe 10mg/simvastatin 20mg tablets (Inegy)	10mg/20mg	£33.42	51.5%	36.6%
Ezetimibe 10mg/simvastatin 40mg tablets (Inegy)	10mg/40mg	£38.98	54.8%	39.2%
Ezetimibe 10mg/simvastatin 80mg tablets (Inegy)	10mg/80mg	£41.21	61%	44%

- Bile acid sequestrants (BASs) (e.g. colestyramine) should be considered if statins or ezetimibe are contraindicated or not tolerated. For longer term treatment consider offering fat-soluble vitamins (A,D and K) and folic acid supplementation.

PACEF Recommendation:
PACEF reviewed colesevelam (Cholestagel) in March 2008 and were concerned about the short-term underpowered nature of the trials, the lack of comparative data with other BAS's and the lack of outcomes data around cardiovascular morbidity and mortality. As a result of this, colesevelam was designated RED-RED. Where a BAS is indicated, for example, in those patients who are unable to tolerate treatment with statins and/or ezetimibe, a better established agent with cardiovascular outcomes data such as cholestyramine should be preferred.

- A specialist may consider the addition of a fibrate or nicotinic acid. Gemfibrozil and statins are not recommended concurrently.

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