NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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What's new this month:

- **Both pramipexole prolonged release tablets (Mirapexin) and ropinirole modified release tablets (ReQuip) have been designated AMBER for patients with Parkinson's Disease (see page 3).**
- **Liraglutide (Victoza) has been approved by NICE for use as a third line alternative to exenatide (Byetta). Both drugs are designated GREEN. Liraglutide is only approved in doses up to 1.2mg once daily. Both drugs must be reviewed 6 months after initiation of treatment and only continued if the patient shows a beneficial metabolic response (defined as a reduction of at least 1.0 percentage point in HbA_{1c} at 6 months) (see page 5).**
- **Denosumab (Prolia) has been approved by NICE as a second line treatment for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. PACEF have approved denosumab for specialist use only as a replacement therapy for teriparatide. Designation: RED (see page 6).**
- **A new systematic review and meta-analysis utilising both published and unpublished data reveals reboxetine (Edronax) to be an ineffective treatment for depression that should no longer be prescribed. Designation: RED-RED (see page 9).**
- **New evidence from the OMEGA study reveals Omacor to be no more effective than placebo post-MI when used within the context of current best-practice. Omacor is RED-RED and should not be used for secondary prevention after myocardial infarction. All existing prescribing should be reviewed and stopped (see page 9).**
- **Further evidence supports the PACEF RED-RED position on glucosamine and glucosamine chondroitin containing products. All remaining prescribing of glucosamine and glucosamine-chondroitin should be reviewed and stopped (see page 10).**

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. 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: DECEMBER 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Denosumab injection (Prolia)	Licensed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.	RED For initiation only by specialists in secondary care
Liraglutide injection (Victoza)	Licensed for the treatment of adults with type 2 diabetes mellitus in combination with**:** (1) Metformin or a sulfonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or a sulfonylurea. (2) Metformin and a sulfonylurea or metformin and a thiazolinedione (glitazone) in patients with insufficient glycaemic control despite dual therapy.	GREEN. N.B. Treatment should primarily be initiated by a diabetologist or a GP with a Special Interest in diabetes (GPSI), although the GREEN status allows for broader GP initiation. Liraglutide initiation should only be considered at Step Three within the context of the NICE initiation criteria as detailed in the text. It should only be used as an alternative to exenatide where exenatide is either not tolerated or inappropriate. Liraglutide should only be used in doses up to 1.2mg
Omacor capsules	Hypertriglyceridaemia Secondary prevention after MI	RED-RED
Omalizumab injection (Xolair)	Licensed for the treatment of severe persistent allergic asthma in children aged 6 to 11 years.	RED-RED
Omalizumab injection (Xolair)	Licensed for the prophylaxis of severe persistent allergic asthma in adults and children over 12	RED
Peginterferon alfa 2a injection (Pegasys)	Licensed in combination with ribavirin for chronic hepatitis C (CHC) or as monotherapy for CHC if ribavirin is not tolerated or contra-indicated	RED
Peginterferon alfa 2b injection (ViraferonPeg)	Licensed in combination with ribavirin for chronic hepatitis C (CHC) or as monotherapy for CHC if ribavirin is not tolerated or contra-indicated	RED
Pramipexole prolonged release tablets (Mirapexin Prolonged Release)	Licensed for the treatment of Parkinson's disease, either alone or as an adjunct to levodopa with dopa-decarboxylase inhibitor	AMBER No shared care guideline required
Reboxetine tablets (Edronax)	Licensed for major depression	RED-RED
Ribavirin tablets (Copegus)	Licensed for the treatment of chronic hepatitis C in combination with interferon alfa or peginterferon alfa	RED
Riibavirin capsules (Rebetol)	Licensed for the treatment of chronic hepatitis C in combination with interferon alfa or peginterferon alfa	RED
Ropinirole modified release tablets (ReQuip XL)	Licensed for the treatment of stable PD in patients transferring from ropinirole immediate release tablets	AMBER No shared care guideline required

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.

GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

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

REVIEW: PRAMIPEXOLE PROLONGED RELEASE TABLETS (MIRAPEXIN) AND ROPINIROLE MODIFIED RELEASE TABLETS (REQUIP XL) FOR PARKINSON'S DISEASE

Both ropinirole modified release tablets (ReQuip XL) and pramipexole prolonged release tablets (Mirapexin Prolonged Release) have been previously designated RED-RED on the Traffic Lights List and have not been approved for use in county. PACEF was asked to review this position within the context of the broader evidence base related to the benefits of once daily therapy in patients with Parkinson's disease (PD).

The evidence to support the use of modified release dopamine agonists, like pramipexole and ropinirole, comes from a series of published studies and reviews which examine the factors affecting medicine adherence in patients with PD. Several observational studies identify a number of factors that may contribute to poor compliance including complex dosage regimens and increased frequency of administration. Once daily dosing regimens appear to be associated with higher adherence rates, improved symptom control and reduced risk of dyskinesia.

Ropinirole MR tablets (ReQuip XL) are licensed for the treatment of idiopathic PD (monotherapy and adjunct therapy) **in patients already taking ropinirole immediate release and in whom adequate symptomatic control has been established.** As a result of this, patients should be initiated and titrated on ropinirole immediate release tablets (generic) before being considered for transfer to the MR formulation. Following a recent 60% price reduction by the manufacturer, ropinirole MR tablets (ReQuip XL) are now lower in price at most doses than the immediate release tablets (see table):

Drug	Dose	Cost/month	Comments
Ropinirole immediate release tablets	1mg three times daily	£23.36	
Ropinirole MR tablets (ReQuip XL)	2mg once daily	£12.54	**2mg MR is £11.06 less per pt/ per month than immediate release**
Ropinirole MR tablets (ReQuip XL)	4mg once daily	£25.09	**4mg is £1.73 more per pt/per month than immediate release.**
Ropinirole immediate release tablets	3mg three times daily	£77.05	
Ropinirole MR tablets (ReQuip XL)	8mg once daily	£42.11	**8mg MR is £34.94 less per pt/month than immediate release.**
Ropinirole MR tablets (ReQuip XL)	10mg once daily	£54.65	**10mg MR is £22.40 less per pt/month than immediate release.**
Ropinirole immediate release tablets	8mg three times a day	£175.48	
Ropinirole MR tablets (ReQuip XL)	24mg once daily	£126.33	**MR is £49.15 less per pt/per month than**

			immediate release.

Pramipexole prolonged release tablets (Mirapexin Prolonged Release) are licensed for the treatment of PD. At present pramipexole PR is comparably priced to immediate release pramipexole, although with patent expiry due in December 2010, this may not remain the case for long.

PACEF Recommendation
As a general rule, PACEF are not supportive of prolonged release formulations as alternatives to immediate release equivalents (particularly where patent expiry results in immediate release equivalents costing considerably less). However, after careful review of the evidence, PACEF are convinced that PR pramipexole and MR ropinirole offer genuine additional benefits for patients with PD, particularly in those with identified compliance problems. Initiation and dose titration should only be undertaken by a specialist in the treatment of PD. Initiation should usually utilise the immediate release formulation prior to consideration of transfer to an equivalent MR/PR dose. As a result of this, both ropinirole modified release tablets (ReQuip XL) and pramipexole prolonged release tablets (Mirapexin Prolonged Release) are designated AMBER; no supporting shared care guideline is required. Recent price changes have resulted in ropinirole MR tablets (ReQuip XL) becoming less expensive than immediate release ropinirole tablets; immediate release pramipexole is also comparably priced to pramipexole PR tablets (Mirapexin Prolonged Release). As a result of this, following initiation on immediate release, there is no reason why MR formulations cannot be used subsequently to improve compliance and disease control.

NICE TECHNOLOGY APPRAISAL 200: *PEGINTERFERON ALFA AND RIBAVIRIN FOR THE TREATMENT OF CHRONIC HEPATITIS C* (PART REVEW OF TECHNOLOGY APPRAISAL GUIDANCE 75 AND 106) (SEPTEMBER 2010)

Key Recommendations

Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C who: (1) have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed or (2) have been co-infected with HIV.

Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with chronic hepatitis C who have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test and are considered suitable for a shortened course of treatment.

PACEF Recommendation:
Peginterferon alfa 2a injection (Pegasys) and peginterferon alfa 2b injection (ViraferonPeg) are approved for use in combination with ribavirin for the treatment of chronic hepatitis C. Designation: RED. Ribavirin tablets (Copegus) and ribavirin capsules (Rebetol) are also approved for use within licensed indications. Designation: RED.

NICE TECHNOLOGY APPRAISAL 201: *OMALIZUMAB FOR THE TREATMENT OF SEVERE PERSISTENT ALLERGIC ASTHMA IN CHILDREN AGED 6 TO 11 YEARS* (OCTOBER 2010)

Omalizumab is not recommended for the treatment of severe persistent allergic asthma in children aged 6 to 11 years.

Children currently receiving omalizumab for the treatment of severe persistent allergic asthma should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the child and/or the child's parents or carers.

PACEF Recommendation:
Omalizumab injection (Xolair) is not recommended for the treatment of severe persistent allergic asthma in children aged 6 to 11 years. Designation: RED-RED. Omalizumab injection (Xolair) has been previously approved by NICE for the prophylaxis of severe persistent allergic asthma in adults and children over 12 (November 2007). Designation: RED.

NICE TECHNOLOGY APPRAISAL 203: *LIRAGLUTIDE FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS (OCTOBER 2010)*

Key Recommendations

Liraglutide 1.2mg daily in combination with either metformin and a sulphonylurea or metformin and a thiazolidinedione (triple therapy) is recommended as an option for the treatment of people with type 2 diabetes. Its place in therapy is defined as the same as that for exenatide, the alternative licensed Glucagon Like Peptide-1 (GLP-1) analogue (as outlined in NICE CG 87 on the management of type 2 diabetes).

Liraglutide 1.2mg daily is also recommended as dual therapy in combination with metformin or a sulphonylurea only if:

- The person is intolerant of either metformin or a sulphonylurea, or treatment with metformin or a sulphonylurea is contraindicated **and**
- The person is intolerant of thiazolidinediones and dipeptidyl peptidase - 4 (DPP-4) inhibitors or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

Treatment with liraglutide 1.2mg daily should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1.0 percentage point in HbA_{1c} at 6 months).

Liraglutide 1.8mg daily is not recommended for the treatment of people with type 2 diabetes. People with type 2 diabetes currently receiving liraglutide who do not meet the criteria for treatment as recommended within the NICE TA or who are receiving daily doses of 1.8mg should have the option to continue their current treatment until they and their clinicians consider it appropriate to stop.

PACEF Recommendations

Liraglutide (Victoza) is designated GREEN. It should primarily be initiated by a diabetologist or a GP with a Special Interest in diabetes (GPSI), although the GREEN status allows for broader GP initiation. NICE Clinical Guideline 87: *Type 2 diabetes – the management of type 2 diabetes* (May 2009) defines a third line role for GLP-1 mimetics (i.e. liraglutide, exenatide) as follows:

Consider adding a GLP-1 mimetic as third line therapy to first line metformin and a second line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c > 7.5% or other higher level agreed with the individual) and the person has: (1) a BMI >35kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological, biochemical or physical problems arising from high body weight or: (2) a BMI < 35kg/m^2 and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities. Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months).

Within this context, exenatide should remain the GLP-1 mimetic of choice. It is estimated that 10 to 12% of patients will be unable to tolerate exenatide; such patients may be appropriate for liraglutide as an alternative. To improve the gastro-intestinal tolerability of liraglutide, treatment should commence on 0.6mg daily. After at least one week, the dose should be increased to 1.2mg. Liraglutide 1.8mg daily is not recommended by NICE and should not be used. Existing patients already receiving the 1.8mg dose can continue treatment where indicated.

All patients treated with exenatide or liraglutide must be reviewed 6 months after initiation of treatment and therapy should only be continued if the patient shows a significant metabolic response (as defined above).

It must be emphasized that NICE and PACEF have only approved exenatide and liraglutide for use within license and NICE guidance. Unlicensed use of either drug in combination with insulin is designated RED-RED.

NICE TECHNOLOGY APPRAISAL 204: *DENOSUMAB FOR THE PREVENTION OF OSTEOPOROTIC FRACTURES IN POSTMENOPAUSAL WOMEN* (OCTOBER 2010)

Key Recommendations

Primary prevention of osteoporotic fragility fractures

1. Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures:

- who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments and

- who have a combination of T-score[1], age and number of independent clinical risk factors for fracture as indicated in the following table.

T-scores (SD) at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable:

	Number of independent clinical risk factors 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 denosumab is not recommended.

Secondary prevention of osteoporotic fragility fractures

2. Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

3. For the purposes of this guidance, independent clinical risk factors for fracture are: parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

4. People currently receiving denosumab for the primary or secondary prevention of osteoporotic fragility fractures who do not meet the criteria specified in recommendations 1.1 or 1.2 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

Notes

Denosumab (Prolia) injection is a monoclonal antibody that reduces osteoclast activity and so reduces bone breakdown. It is licensed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Denosumab is administered as a single sub-cutaneous injection into the thigh, abdomen or back of the arm. The recommended dose is 60mg every 6 months and the annual cost is £366pa.

The trial evidence centres around a single trial: the Fracture Reduction Evaluation of Denosumab in Osteoporosis every six Months study (FREEDOM). FREEDOM is a multicentre, double-blind, placebo controlled trial involving 7,868 postmenopausal women aged 60-90 years with T scores of less than -2.5 SD and greater than -4.0 SD at lumber spine, total hip or both. Women entering the trial were randomly assigned to either denosumab 60mg sc inj every 6 months for 3 years or placebo. All participants took daily calcium and vitamin D. The primary outcome was incidence of new radiographically diagnosed vertebral fractures with secondary outcomes of time to first non-vertebral fracture and time to first hip fracture. Results showed the incidence of new radiographically diagnosed vertebral fractures was 2.3% in the

denosumab group and 7.2% in the placebo group. Similar reductions in incidence were observed with non-vertebral fracture and hip fracture.

Unfortunately, there are no head-to-head clinical trials comparing denosumab with any relevant comparator (e.g. oral bisphosphonates, strontium ranelate, raloxifene, teriparatide, zoledronate). NICE based their decision on a meta-analysis undertaken by the manufacturer of the relative risks for all fracture endpoints for denosumab, strontium ranelate, raloxifene, teriparatide and zoledronate compared to placebo. The meta-analysis showed that all treatments reduced the risk of **morphometric vertebral fractures** compared to placebo. Denosumab, strontium ranelate and zoledronate were all associated with a statistically significant decrease in the risk of **clinical vertebral fractures.** Denosumab, strontium ranelate, teriparatide and zoledronate were all associated with a statistically significant decrease in the risk of **non-vertebral fractures.** Only denosumab and zoledronate were associated with statistically significant decreases in the risk of **hip fractures.**

Using a cost-model generated by the manufacturer, NICE conclude that denosumab is cost-effective for both primary and secondary prevention, although the high incremental cost effectiveness ratio (ICER) for primary prevention makes it appropriate only as a second line option after oral bisphosphonates. The ICER for secondary prevention is lower, but still necessitates a second line position after oral bisphosphonates.

A cost comparison between denosumab and available alternatives reveals that only teriparatide has a higher annual cost:

Product	**Licensed Indication and Recommended Dosage**	**Cost of 12 months treatment**
Alendronate 70mg tabs	**Treatment of postmenopausal osteoporosis.** **One tablet a week.**	**£13.65**
Denosumab injection 60mg (Prolia)	One sub-cutaneous 60mg injection every 6 months.	£366
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	£80.47
Risedronate 35mg tabs (Actonel Once a Week)	Treatment of postmenopausal osteoporosis. One tablet a week.	£248.56 NB Patent expiry is pending in December 2010. Lower cost risedronate is imminent
Raloxifene (Evista) 60mg tablets	Treatment and prevention of postmenopausal osteoporosis 60mg once daily	£221.78
Strontium ranelate (Protelos) 2g sachet	Treatment of postmenopausal osteoporosis to reduce risk of vertebral and hip fractures 2g once daily	£332.80
Teriparatide (Forsteo) injection 250mcg per ml, 3ml pre-filled syringe	Treatment of osteoporosis in postmenopausal women 20mcg daily by SC injection	£3,534.44

(Prices quoted are from the *Drug Tariff* and MIMS, December 2010)

PACEF Recommendations:
PACEF is concerned about the lack of comparative trail data between denosumanb and alternative second line treatments for osteoporosis. The relatively high ICERs, particularly for primary prevention, and the high comparative cost, necessitate an initial conservative approach to the introduction of this treatment. As a result, denosumab injection is initially approved as a replacement therapy for teriparatide injection (Forsteo) for use in secondary care only. Designation: RED. Teriparatide is ten times the cost of denosumab and requires daily SC injection rather than 6 monthly SC injection. A wider role for denosumab will be considered at a later date as further evidence emerges.

NEW TRIALS IN BRIEF

REBOXETINE (EDRONAX): AN INEFFECTIVE ANTIDEPRESSANT?

This systematic review and meta-analysis of 13 double-blind RCTs (4098 adults) compared reboxetine to placebo or an SSRI in the management of depression. Data on 74% of the patients analysed within the study were previously unpublished. The authors compared the effect sizes for the published, unpublished and full dataset. Using the full dataset reboxetine showed no benefit over placebo and was inferior to SSRIs for remission and 50% response rates. Using only published data reboxetine was reported to be more effective than placebo and similar in efficacy to SSRIs. This reveals a striking example of publication bias which overestimates the benefit of reboxetine and underestimates the harm.

PACEF Comment:
This study suggests that reboxetine is not an effective treatment for depression and should not be prescribed. Clinicians should identify and review existing patients on reboxetine and, in discussion with the patient, consider whether reboxetine is still an appropriate treatment choice. Reboxetine (Edronax) is re-classified from AMBER to RED-RED. Existing patients can continue with treatment until they or their clinician consider it appropriate to stop.

Reference:
Eyding D et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010;341:c4737

OMACOR AND THE OMEGA STUDY

This RCT compared Omacor 1g daily to placebo for 1 year in 3,851 post-MI patients treated in Germany according to current guidelines. There was no statistically significant difference between Omacor and placebo in the primary outcome of sudden death (1.5% vs 1.5%, P=0.84). There were also no statistically significant differences in total mortality (4.6% vs. 3.7%; P=0.18) or in major adverse cerebrovascular and cardiovascular events (10.4% vs. 8.8%; P=0.1) or revascularisations (27.6% vs. 29.1%; P=0.34).

PACEF Comment:
PACEF have never accepted the recommendation in NICE Clinical Guideline 48 *MI: secondary prevention* (May 2007) that Omacor should be used post-MI for patients unable to consume sufficient quantities of oily fish. Our argument has always been that trial evidence evaluating Omacor within the context of current guidelines (e.g. optimum BP control, concurrent statin therapy etc) was needed

before a convincing case could be made. OMEGA provides that contextual data and reveals Omacor to be an unnecessary additional treatment in a patient group already managing complex multi-component regimes. Omacor is designated RED-RED. All remaining patients taking Omacor for secondary prevention after MI should be reviewed as a matter of urgency with a view to discontinuing treatment wherever possible. Existing spend on Omacor is approaching £200,000pa across Lincolnshire; this could be markedly reduced through the implementation of this guidance.

Reference
Rauch B et al. OMEGA, a randomised placebo controlled trial to test the effect of highly purified omega 3 fatty acids on top of modern guideline adjusted therapy after myocardial infarction. Published online before print Nov 8 2010; doi 10.1161/CIRCULATIONAHA.110.948562

GLUCOSAMINE: THE FINAL CHAPTER?

This meta-analysis of large RCTs (defined as more than 200 participants) assessed the effect of glucosamine, chondroitin or their combination with placebo in knee or hip osteoarthritis. Neither treatment (separately or in combination) produced an improvement in pain score compared to placebo which was likely to be clinically meaningful (pre-defined as a difference of at least 0.9cm on a 10cm visual analogue scale).

PACEF Comment:
This meta-analysis supports the decision by NICE that glucosamine and chondroitin do not bring sufficient benefit at a population level to justify NHS prescription. Glucosamine products remain classified by PACEF as RED-RED and should not be prescribed. Many patients taking glucosamine have already been reviewed and asked to purchase further supplies (if considered beneficial) from their local community pharmacy, supermarket or health food store; remaining patients need to be reviewed as a matter of urgency with a view to discontinuing prescribed glucosamine wherever possible.

Reference:
Wandel S et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010;341:c4675

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

Tamoxifen for breast cancer: drug interactions involving CYP2D6, genetic variants, and variability in clinical response.

- A population-based cohort study on SSRI antidepressants and breast-cancer mortality in women receiving tamoxifen found that the risk of death from breast cancer increased with the length of concomitant treatment with paroxetine (a potent inhibitor of CYP2D6), but not with other SSRIs.
- It is recommended that strong CYP2D6 inhibitors should be avoided whenever possible in patients taking tamoxifen. Concomitant use of medicines known to be potent CYP2D6 inhibitors should be avoided whenever possible in patients treated with tamoxifen. Examples of such drugs include **paroxetine, fluoxetine, bupropion, quinidine,** and **cinacalcet.**

Memantine pump device (Ebixa): Risk of medication errors

- Several cases of administration error resulting in overdose with the new memantine pump device have been reported. The medication errors resulted

from confusion between doses delivered by the new pump device and doses delivered by the dropper.

Advice for healthcare professionals:

- There are differences in dose delivery between the pump device and dropper device for memantine;
- One actuation of the pump device delivers 0.5 mL of solution, corresponding to 5mg memantine. The maximum daily dose is 20 mg or four pump actuations, whereas 40 drops could be given with the dropper.
- Please be vigilant regarding dose delivery for memantine products, particularly during the transition period from the dropper device to the new pump device.

PACEF Comment:
This safety alert should have limited impact in Lincolnshire as memantine (Ebixa) is not approved by NICE for the treatment of Alzheimer's Disease unless as part of a clinical trial. As a result, memantine is designated RED-RED. NICE are currently reviewing their guidance on the treatment of dementia; the position of memantine will be reviewed following publication.

Oral bisphosphonates: oesophageal cancer risk—insufficient evidence of a link

- There is clear evidence that nitrogen-containing bisphosphonates (i.e., alendronic acid, ibandronic acid, and risedronate) can cause oesophageal irritation and reactions.
- After reports of oesophageal cancer in association with oral bisphosphonates several studies were commissioned as part of a Europe-wide review to try to establish whether such a link exists.
- This review concluded that given the limitations of one study and a lack of supporting evidence from other studies, there is insufficient evidence to confirm a link between oral bisphosphonate use and oesophageal cancer.
- Furthermore, patients receiving oral bisphosphonates are more likely to be monitored for oesophageal reactions than those not receiving bisphosphonates, which may result in an increased detection of oesophageal cancer in patients receiving bisphosphonates.

Advice for healthcare professionals:

- Alendronate and oral ibandronate should not be given to patients with abnormalities of the oesophagus and/or other factors which delay oesophageal emptying such as stricture or achalasia. Risedronate should be used with caution in such patients
- Alendronate, oral ibandronate, and risedronate should be used with caution in patients with active or recent upper gastrointestinal problems.
- In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate and oral ibandronate on an individual basis.

PACEF Comment
In September 2010 PACEF reviewed a case control study published in the BMJ which suggested a possible association of bisphosphonate use with an increased risk of oesophageal cancer. PACEF advice at the time was to advise patients of the importance of adhering to the strict dosage

instructions for oral bisphosphonates to minimize potential oesophageal irritation or damage.

Tiotropium: safety studies of Spiriva Respimat

- The MHRA has previously highlighted the conflicting findings of a number of recent studies on the safety of inhaled anticholinergic drugs.
- Tiotropium is a long-acting muscarinic receptor antagonist that is licensed as a prescription-only medicine for maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD).
- Two formulations are available as the brand name Spiriva: a capsule containing 18 micrograms tiotropium delivered via a HandiHaler taken once daily; and a soft-mist Respimat inhaler that delivers 2·5 micrograms tiotropium per actuation taken as two puffs once a day at the same time of the day.
- A large 4-year placebo-controlled randomised double-blind trial concluded that tiotropium delivered via HandiHaler was associated with a non-significantly decreased risk of all-cause mortality, myocardial infarction, or stroke compared with placebo.
- A recently completed safety study that compared Spiriva Respimat▼ with placebo in patients with COPD found that lung function, COPD exacerbations, and quality of life were improved by 5 micrograms Respimat, but a numerical increase was seen in all cause mortality compared with placebo.
- The underlying reasons for the apparent difference are unclear, and may be a chance finding; further studies are ongoing.

Advice for healthcare professionals:

- Spiriva Respimat should be used with caution in patients with known cardiac rhythm disorders.

PACEF Recommendation: Safety of Spiriva Respimat

A recent safety study covered by the MHRA in the *Drug Safety Update* for November 2010 reported that Spiriva Respimat was associated with a non-significant increase in all-cause mortality compared with placebo. By contrast, Spiriva Handihaler was associated with a decrease in all-cause mortality compared with placebo. This may be a chance finding of little significance, but pending further study, safety concerns tend to support Spiriva Handihaler as the preferred Long Acting Muscarinic Agent of choice.

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