Arden and Greater East Midlands Commissioning Support Unit in association with Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services, United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 10; Number 3 **February 2016**

What's new this month?

- **For women with postmenopausal osteoporosis who have difficulty swallowing alendronic acid 70mg tablets, careful consideration should be given to alternative options. For those at low risk of falling due to immobility (i.e. patients confined to bed or unable to get up from a chair unaided), serious consideration should be given to discontinuing bisphosphonate therapy altogether. Where the decision is taken to continue with alendronate therapy, 70mg effervescent tablets (*Binosto*) should be preferred to the licensed liquid preparation (see page 3).**
- **As the dose and strength of colecalciferol 1000 IU and 25,000IU tablets (*Stexerol-D3*) are at variance from the standard doses agreed as part of local guidance on the treatment of vitamin D deficiency, the products are designated RED-RED and are not approved for inclusion in local treatment guidance or the *Lincolnshire Joint Formulary* (see page 3).**
- ***Thick & Easy Clear* is approved for use as an alternative xanthan based drink thickener to *Resource ThickenUp Clear* for patients with swallowing difficulties. It should only be prescribed following an assessment by a Speech and Language Therapist or a Dysphagia Trained Nurse and is designated AMBER. Prescribers should use the monthly usage table below to determine the appropriate quantity of thickener to be prescribed each month. Individual dose sachets should not usually be prescribed as they are significantly more costly than multiple scoop tins (see page 5).**
- **Contrary to PACEF guidance, tapentadol products are approved for use in Nottinghamshire within the context of local pain guidance. In the spirit of local cooperation, PACEF have re-designated tapentadol immediate-release tablets (*Palexia*) and prolonged-release tablets (*Palexia SR*) as AMBER subject to initiation by the Nottinghamshire Pain Team. Both products remain RED-RED for all other indications and should not be initiated in Lincolnshire (see page 8).**

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SUMMARY OF PACEF DECISIONS: *JANUARY 2016 UPDATE*

Drug	**Indication(s)**	**Traffic Light and *Joint Formulary* Status**
Alendronic acid 70mg effervescent tablets (Binosto)	For the treatment of postmenopausal osteoporosis	GREEN For patients unable to swallow standard alendronic acid 70mg tablets. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Colecalciferol 1000iu and 25000iu tablets *(Stexerol-D3)*	For the prevention and treatment of vitamin D deficiency in adolescents, adults and the elderly. Also indicated as an adjunct to treatment for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*.
Tapentadol immediate-release tablets (Palexia)	Licensed for the relief of moderate to severe acute pain in adults.	RED-RED in Lincolnshire. Not approved for inclusion in the *Lincolnshire Joint Formulary.* AMBER subject to initiation by the Nottinghamshire Pain Team.
Tapentadol prolonged-release tablets (Palexia SR)	Licensed for the management of severe chronic pain in adults.	RED-RED in Lincolnshire. Not approved for inclusion in the *Lincolnshire Joint Formulary.* AMBER subject to initiation by the Nottinghamshire Pain Team.
Thick and Easy Clear powder (Fresenius Kabi)	Food and drink thickener for patients with dysphagia	AMBER following assessment by a Speech and Language Therapist or Dysphagia Trained Nurse. Approved for inclusion in the *Lincolnshire Joint Formulary*.

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 PACEF website (http://lincolnshire-pacef.nhs.uk). Electronic copies of the *PACE Bulletin* are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk.

Google searching can be a quick and effective way of finding back numbers of the *PACE Bulletin* relevant to a specific topic of interest. Searchers are advised to use the official version of the *Bulletin* available from the PACEF website rather than depend on a potentially unreliable draft or variant found through Google or an alternative search engine.
The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

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.**

RAPID DRUG ASSESSMENT: *ALENDRONIC ACID 70MG EFFERVESCENT TABLETS (BINOSTO)*

For women with postmenopausal osteoporosis who have difficulty swallowing alendronic acid 70mg tablets, an effervescent 70mg tablet formulation (*Binosto*) has been approved for use.

Alendronic acid 70mg effervescent tablets (*Binosto*) is a new effervescent formulation of once weekly alendronate licensed for the treatment of postmenopausal osteoporosis. A cost comparison reveals that it is significantly higher is cost that once weekly generic alendronic acid 70mg, but lower cost than the licensed oral solution.

Product	Dose	Cost (£) 28 days
Alendronic acid 70mg effervescent tablets (*Binosto*) (Internis Pharmaceuticals Ltd)	70mg once a week	£22.80 (4)
Alendronic acid 70mg tablets (generic)	70mg once a week	£0.92 (4)
Alendronate 70mg/100ml oral solution unit dose	70mg once a week	£27.29 (4 x 100ml)

PACEF Recommendation:
Alendronic acid 70mg tablets (generic) remains the first line bisphosphonate of choice in most women for the treatment of postmenopausal osteoporosis. These tablets should be swallowed whole with plenty of water while sitting or standing with the patient continuing to stand or sit upright for at least 30 minutes after taking the tablet. For patients who have difficulty swallowing tablets, careful consideration should be given to alternative options. For those at low risk of falling due to immobility (i.e. patients confined to bed or unable to get up from a chair unaided), serious consideration should be given to discontinuing bisphosphonate therapy altogether. Where the decision is taken to continue with alendronate therapy, 70mg effervescent tablets (*Binosto*) should be preferred. Alendronic acid 70mg effervescent tablets (*Binosto*) are designated GREEN and approved for use through the *Lincolnshire Joint Formulary.* Alendronate 70mg/100ml oral solution unit dose (generic) remains on the *Joint Formulary*, but now have a very limited role.

RAPID DRUG ASSESSMENT: *COLECALCIFEROL 1000IU AND 25000IU TABLETS (STEXEROL-D3)*

As the dose and strength of colecalciferol 1000 IU and 25,000IU tablets (*Stexerol-D3*) are at variance from the standard doses agreed as part of local guidance on the treatment of vitamin D deficiency, the products are designated RED-RED and are not approved for inclusion in local treatment guidance or the *Lincolnshire Joint Formulary*.

The table below summarizes current PACEF guidance on the treatment of vitamin D deficiency (for further detail see *PACE Bulletin* Vol 9 No13 (September 2015)).

Level of deficiency	25 hydroxyvitamin D level	Recommended treatment
Severe deficiency (associated with osteomalacia including rickets in children and osteoporosis and fractures in adults)	<25 nmol/l 25 hydroxyvitamin D	Capsule formulations: Dose: 40,000 IU weekly for 7 weeks. Preferred products: *Aviticol* 20,000IU capsules *Fultium D3* 20,000IU capsules *Plenachol* 20,000IU and 40,000IU

		capsules Liquid formulations Dose: 50,000IU weekly for 6 to 8 weeks. Preferred products: *InVita D3* oral solution 25,000IU in 1ml *Thorens* oral solution 25,000IU in 2.5ml
Deficiency associated with disease risk	25-50 nmol/l 25 hydroxyvitamin D	If symptoms are severe, treat with preferred products and licensed doses detailed above. If physical symptoms are milder, lower doses are indicated Dose: 800-1600 IU daily for 12 weeks. Preferred products: *Desunin* 800IU tablets *Fultium D3* 800IU capsules
Insufficiency	50-75nmol/l 25 hydroxyvitamin D	If physical symptoms are present, prescribe 800-1600 IU daily for 12 weeks (as detailed above). If patient has no physical symptoms, consider lifestyle advice including: increased dietary intake and safe sun exposure (see *PACE Bulletin* Vol 6 No 6 Prevention of vitamin D deficiency in at-risk groups (May 2012)).
Replete	>75nmol/l 25 hydroxyvitamin D	No treatment necessary

As part of the most recent review, doses were standardized around an existing range of licensed and readily available products.

Colecalciferol 1000 IU and 25,000IU tablets (*Stexerol-D3*) hold a marketing authorisation for the prevention and treatment of vitamin D deficiency in adolescents, adults and the elderly. The product is also indicated as an adjunct to treatment for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency. Adult doses are as follows:

Treatment of severe deficiency (serum levels < 25ng/ml): 50,000iu weekly for 6 weeks or 3000—4000iu daily for 10—12 weeks; maintenance, 25,000iu monthly or 1000iu daily.
Prevention of deficiency: 25000iu monthly or 1000iu daily.

Unfortunately, these doses are different from the standard doses of existing PACEF approved *Formulary* products for the treatment of vitamin D deficiency. To introduce products with doses at variance from local guidance at this stage will simply serve to add unnecessary complication to an already complex treatment area.

PACEF Recommendation
As the dose and strength of colecalciferol 1000 IU and 25,000IU tablets (*Stexerol-D3*) are at variance from the standard doses agreed as part of local guidance on the treatment of vitamin D deficiency, the products are designated RED-RED and are not approved for inclusion in local treatment guidance or the *LincoInshire Joint Formulary*. Prescribers are reminded of the key points around the prescribing of vitamin D reiterated below.

Treatment

- All of the preferred first-line products named in the table above are designated GREEN and are approved for use through the *Lincolnshire Joint Formulary.*
- **In order to prevent confusion with similar strength unlicensed food supplements, all colecalciferol products should be prescribed by preferred brand name. Prescribers are asked to review existing patients receiving vitamin D supplementation to ensure that preferred products designated by brand name are being prescribed wherever possible.**
- Unlicensed vitamin D formulations classed as either unlicensed specials or food supplements should only be used as a last resort when the patient's clinical needs cannot be met using a licensed product.

NEW PRODUCT ASSESSMENT: *THICK & EASY CLEAR*

***Thick & Easy Clear* is approved for use as an alternative xanthan based drink thickener to *Resource ThickenUp Clear* for patients with swallowing difficulties.**

Thick & Easy Clear is a new xanthan gum based drink thickener designed to increase the safety of swallowing in patients suffering from oropharyngeal dysphagia. It can be used to modify the consistency of drinks, helping people with dysphagia to control their swallowing more effectively and to keep well hydrated.

While there are many food and drink thickening products available, the majority are maize starch based and primarily suited to thickening food rather than drink. Where drink thickening is required, xanthan gum containing products are often preferred. Until recently, *Resource ThickenUp Clear* was the only xanthan gum based product available in the UK. This product has been approved for use through the *Lincolnshire Joint Formulary* and designated AMBER subject to assessment by a Speech and Language Therapist (SLT) or Dysphagia Trained Nurse. Most recently *Thick & Easy Clear* has been launched by Fresenius Kabi and is already in use within United Lincolnshire Hospitals.

Patients with dysphagia are at higher risk of aspiration pneumonia, choking and dehydration. Traditional maize starch based food thickeners include: *Multi-Thick, Nutilis, Nutilis Clear, Resource Thickenup, Thick and Easy, Thicken Aid, Thixo-D* and *Vitaquick.* Until recently starch based thickeners were the only option in terms of thickening of drinks. This had a number of disadvantages:

(1) starch based thickeners alter the texture and taste of the liquid rendering it unappetising for some people. Clear drinks, like water, are rendered opaque. This can deter some patients from drinking or finishing a drink once started.
(2) starch based thickeners continue to thicken over time rendering a drink progressively thicker as time goes on. This can result in patients starting a drink, but never finishing one.
(3) people with dysphagia can have a tendency to hold food or drink in their mouth longer than non-dysphagic patients. Amylase enzymes in saliva can begin to break down maize starch in the mouth before it can be swallowed. As a result of this, a thickened drink can become thinner in the mouth, re-creating swallowing difficulties.

The advantages of drink thickening with xanthan gum containing products include:

(1) Xanthan gum based products are visually clear and flavourless and do not compromise the look, smell, texture and flavour of the thickened drink.
(2) Xanthan gum thickened drinks are visually more appealing and appetising.

(3) Xanthan gum thickened drinks do not continue to thicken over time.
(4) Xanthan gum is more amylase resistant than maize starch and is less likely to be broken down by saliva.
(5) Xanthan gum based products are no more expensive than the maize starch based alternatives, particularly at syrup consistency.
(6) Improved palatability of xanthan gum thickened drinks can help to improve patient hydration.

Food and drink thickeners should only be prescribed in response to an assessment conducted by a Speech and Language Therapists (SLT) or a Dysphagia Trained Nurse.

A cost comparison of all of the available food and drink thickening products reveals that, in terms of cost per dose, they are all comparably priced at the syrup consistency. Dose per dose, *Thick & Easy Clear* emerges as marginally more expensive that *Resource ThickenUp Clear.*

	Unit size and cost	No of doses per tin	Cost per dose
Multi-thick (maize starch)	250g -£4.83	62.5	£0.08
Nutilis Powder (maize starch)	300g - £4.92	50-75	£0.07 - £0.10
Nutilis Clear (maize starch)	175g - £8.46	87.5	£0.10
Resource Thickenup (maize starch)	75 x 4.5g sachet - £17.86 227g - £4.66	 50.44	24p per sachet £0.09
***Resource ThickenUp Clear* (xanthan gum)**	**24 x 1.2g sachet - £5.28** **125g - £8.46**	 **104**	**22p per sachet** **£0.08**
Thick & Easy (maize starch)	225g - £5.06	50	£0.10
***Thick & Easy Clear* (xanthan gum)**	**126g - £8.80**	**90**	**£0.10**
Thicken Aid (maize starch)	100 x 9g sachet - £22.40 225g -£3.71	 50	22p per sachet £0.07
Thixo-D Original (maize starch)	375g - £5.79	75	£0.08
Vitaquick (maize starch)	300g - £7.05 2kg -£38.92	100 667	£0.07 £0.06

	Stage 1 dysphagia (syrup)	**Stage 2 dysphagia (custard)**	**Stage 3 dysphagia (pudding)**
Multi-thick (maize starch)	1.5 scoops (4g) in 100ml	2 - 2.5 scoops (5.4-6.75g)	2.5 – 3.5 scoops (6.75 – 9.45g) in 100ml
Nutilis Powder (maize starch)	1 – 1.5 scoops (4-6g)in 100ml	1.5 – 2 scoops (6-8g) in 100ml	2-3 scoops (8-10g) in 100ml
Nutilis Clear (maize starch)	0.5 scoops (2g) in 100ml	1.5 scoops (6g) in 100ml	3 scoops (12g) in 100ml
Resource Thickenup (maize starch)	1 scoop (4.5g) in 100ml	1.5 scoops (6.75g) in 100ml	2 scoops (9g) in 100ml
***Resource ThickenUp Clear* (xanthan gum)**	**1 scoop (1.2g) in 100ml**	**2 scoops (2.4g) in 100ml**	**3 scoops (3.6g) in 100ml**
Thick and Easy (maize starch)	1 scoop (4.5g) in 100ml	1.5 scoops (6.8g) in 100ml	2 scoops (9g) in 100ml
***Thick and Easy Clear* (xanthan gum)**	**1 scoop (1.4g) in 100ml**	**2 scoops (2.8g) in 100ml**	**3 scoops (4.2g) in 100ml**
Thicken Aid (maize starch)	1 scoop (4.5g) in 100ml	1.5 scoops (6.75g) in 100ml	2 scoops (9g) in 100ml
Thixo-D Original (maize starch)	1 scoop (5g) in 100ml	1.25 scoops (6.25g) in 100ml	1.5 scoops (7.5g) in 100ml
Vitaquick (starch powder)	1 scoop (5g) in 150ml	2 – 2.5 scoops (10g – 12.5g) in 150ml	4 scoops (20g) in 150ml

Definitions

Stage 1 (syrup)	**Stage 2 (custard)**	**Stage 3 (pudding)**
Can be drunk through a straw.	Cannot be drunk through a straw.	Cannot be drunk through a straw.
Can be drunk from a cup if preferred.	Can be drunk from a cup.	Cannot be drunk from a cup.
Leaves a thin coat on the back of a spoon.	Leaves a thick coat on the back of a spoon.	Needs to be taken with a spoon.

Resource ThickenUp Clear: Likely monthly usage (28 days) and monthly cost

Fluid amount per day	**Stage 1 (syrup)**	**Stage 2 (custard)**	**Stage 3 (pudding)**
200ml	1 tin (£8.46)	2 tins (£16.92)	2 tins (£16.92)
600ml	2 tins (£16.92)	4 tins (£33.84)	5 tins (£42.30)
1000ml	3 tins (£25.38)	6 tins (£50.76)	9 tins (£76.14)
1500ml	5 tins (£42.30)	9 tins (£76.14)	13 tins (£109.98)
2000ml	6 tins (£50.76)	11 tins (£93.06)	17 tins (£143.82)

Thick & Easy Clear: Likely monthly usage (28 days) and monthly cost.

Fluid amount per day	**Stage 1 (syrup)**	**Stage 2 (custard)**	**Stage 3 (pudding)**
1000ml	3 tins (£26.40)	6 tins (£52.80)	9 tins (£79.20)
1500ml	5 tins (£44.00)	9 tins (£79.20)	14 tins (£123.20)
2000ml	6 tins (£52.80)	12 tins (£105.60)	19 tins (£167.20)

It is reasonable to assume that a person with stage 1 dysphagia requiring syrup consistency fluids will use approximately 2 tins per month at a cost of £16.92 to £17.60.

Some patients may require thickened fluids on a long-term basis; others only require them short-term. Some patients have a swallowing disability that comes and goes and may only require thickeners at certain times (e.g. some patients with multiple sclerosis). The majority of patients who need their drinks thickened must have **all** fluids thickened to the required viscosity until they are deemed safe to recommence normal fluids. The length of time that thickened fluids are required varies from a few days to several months to the end of life in some cases.

PACEF Recommendation

In terms of cost per dose, all of the food and drink thickeners are comparably priced. This means that, at syrup consistency, where the number of scoops required per 100ml is broadly comparable at 1 to 1.5 scoops, the price of each product is very similar. However, at thicker consistencies, where a variable number of scoops are required, some products emerge as more expensive than others. Comparing *Resource ThickenUp Clear* with *Thick & Easy Clear*, the products emerge as broadly similar in cost with *Resource ThickenUp Clear* emerging as slightly lower in price. *Thick & Easy Clear* is approved for use as an alternative to *Resource ThickenUp Clear*; designation: AMBER. It should only be prescribed following an assessment by a Speech and Language Therapist or a Dysphagia Trained Nurse. It is approved for inclusion in the *Lincolnshire Joint Formulary.* Prescribers should use the monthly usage table to determine the quantity of thickener to be prescribed each month. Individual dose sachets should not usually be prescribed as they are significantly more costly than multiple scoop tins.

DIAMORPHINE SHORTAGE

On December 31st 2015, all practices received an alert sent out by NHS England informing them of a national shortage of the raw materials required to manufacture all strengths of diamorphine injection. The manufacturers intend to continue to supply limited amounts to pharmaceutical wholesalers as long as stocks hold out, although supply around most if not all strengths is now exhausted. Clinicians are advised to contact the patient's preferred pharmacy by telephone before writing prescriptions to check the availability of the required strength or alternative opiate.

TAPENTADOL AND NOTTINGHAMSHIRE PAIN GUIDANCE

Tapentadol is an opioid analgesic combining two mechanisms of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition. The prolonged-release tablets (*Palexia SR*) are licensed for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics. The immediate-release tablets (*Palexia*) are licensed for the relief of moderate to severe acute pain in adults.

PACEF reviewed both products in January 2012 and both were designated RED-RED. Concern was expressed around the lack of comparative data between tapentadol and lower cost opioid alternatives such as modified release morphine. It was acknowledged that the drug emerged as non-inferior to oxycodone in trials and was better tolerated at a similar cost, but both oxycodone and tapentadol remain expensive in comparison to lower cost alternatives. A similar review was undertaken by Nottinghamshire Area Prescribing Committee at about the same time, but reached a different conclusion.

PACEF Recommendation:
Contrary to the PACEF decision, tapentadol products are approved for use in Nottinghamshire within the context of local pain guidance. In the spirit of local cooperation, PACEF have re-designated tapentadol immediate-release tablets (*Palexia*) and prolonged-release tablets (*Palexia SR*) as AMBER subject to initiation by the Nottinghamshire Pain Team. Both products remain RED-RED for all other indications and should not be initiated in Lincolnshire.

UPDATED SHARED CARE GUIDELINE: *MIDODRINE 2.5MG AND 5MG TABLETS FOR THE TREATMENT OF SEVERE ORTHOSTATIC HYPERTENSION DUE TO AUTONOMIC DYSFUNCTION AND UNLICENSED USE FOR THE TREATMENT OF SEVERE ORTHOSTATIC HYPOTENSION OR SYNCOPE IN THE ABSENCE OF AUTONOMIC DYSFUNCTION*

PACEF have approved an updated version of the midodrine shared care guideline prepared in conjunction with ULH Cardiology. The SCG is available through the PACEF website or by contacting Cathy Johnson on cathy.johnson@ardengemcsu.nhs.uk

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (DECEMBER 2015)

THALIDOMIDE: REDUCED STARTING DOSE IN PATIENTS OLDER THAN AGE 75 YEARS

- In patients older than age 75 years, a 100 mg/day starting dose of thalidomide is now recommended to minimise the risk of adverse drug reactions
- In these patients, the starting dose of melphalan should be 0.1–0.2 mg/kg daily, according to baseline bone-marrow reserve and renal function

- Prescribers should be aware that even with a reduced starting dose of thalidomide, this age-group may be at higher risk of serious adverse reactions compared with younger patients.
- The recommended starting dose of thalidomide remains 200 mg once a day for patients age 75 years or younger.

MYCOPHENOLATE MOFETIL, MYCOPHENOLIC ACID: NEW PREGNANCY-PREVENTION ADVICE FOR WOMEN AND MEN

A review of worldwide cases of congenital malformations after exposure to mycophenolate during pregnancy has confirmed an increased rate of congenital malformations and spontaneous abortions compared with other immunosuppressants. Spontaneous abortions have been reported in 45–49% of pregnant women exposed to mycophenolate mofetil, compared with 12–33% with other immunosuppressants.

Previously only ear malformations were linked to mycophenolate, but prospectively gathered data has now identified a range of disorders including:

- Congenital heart disease, such as atrial and ventricular septal defects
- Facial malformations, including cleft lip and cleft palate, micrognathia, and hypertelorism of the orbits
- Eye abnormalities
- Finger malformations
- Tracheo-oesophageal malformations
- Nervous system malformations, such as spina bifida
- Renal abnormalities

Key updated safety advice for healthcare professionals:

- Mycophenolate mofetil or mycophenolic acid should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection.
- Physicians should ensure that women and men taking mycophenolate mofetil and mycophenolic acid understand: the risk of harm to a baby; the need for effective contraception; the need to plan for pregnancy and change treatment as necessary; and the need to immediately consult a physician if there is a possibility of pregnancy.
- Mycophenolate mofetil or mycophenolic acid treatment should only be initiated in women of child bearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy.
- Mycophenolate mofetil or mycophenolic acid should only be given to women of childbearing potential who are using highly effective contraception
- Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment.
- Men (including those who have had a vasectomy) should use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products
- Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose.

Updated advice on pregnancy testing

- Before starting mycophenolate mofetil treatment, women of childbearing potential should have a negative pregnancy test result to exclude unintended exposure of the embryo to mycophenolate.
- Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended. The second test should be done 8–10 days after the first one and

immediately before starting mycophenolate mofetil. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported).
- Results of all pregnancy tests should be discussed with the patient.
- Patients should be instructed not to stop treatment but to consult their physician immediately should pregnancy occur.

Reporting of suspected adverse reactions
Suspected adverse reactions to mycophenolate mofetil, including adverse pregnancy outcomes, should be reported to us on a Yellow Card.

PACEF Recommendation:
Mycophenolate mofetil and mycophenolate sodium preparations are regularly prescribed by Lincolnshire GPs as part of local shared care guidelines supporting patients following organ transplantation. Shared Care Guidelines will be updated to reflect the significant risk to the unborn child if mycophenolate is continued or initiated during pregnancy.

BISPHOSPHONATES: VERY RARE REPORTS OF OSTEONECROSIS OF THE EXTERNAL AUDITORY CANAL

Osteonecrosis of the external auditory canal has been reported very rarely (fewer than 1 in 10 000 patients) with bisphosphonates,mainly in association with long-term therapy (2 years or longer). Examples of bisphosphonates prescribed in Lincolnshire include: alendronic acid, ibandronic acid and risedronate sodium.

Evidence from the clinical literature and from cases reported to medicines regulators, including one report received via the UK Yellow Card scheme, supports a causal association between bisphosphonates and osteonecrosis of the external auditory canal. Product information is being updated to include advice for healthcare professionals and patients. Most cases were linked with long-term bisphosphonate therapy of 2 years or longer, and usually involved additional risk factors such as steroid use; chemotherapy; infection, a recent ear operation or cotton-bud use. The number of cases of osteonecrosis of the external auditory canal reported in association with bisphosphonates is low compared with the number of cases reported of bisphosphonate-related osteonecrosis of the jaw, a well-established side effect of bisphosphonates

The available data do not support a causal relation between osteonecrosis of the external auditory canal and denosumab (*Prolia*). However, this possible risk is being kept under close review, given that denosumab is also known to be associated with osteonecrosis of the jaw.

Advice for healthcare professionals:
- The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma
- Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma
- Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate treatment
- Report any cases of osteonecrosis of the external auditory canal suspected to be associated with bisphosphonates or any other medicines, including denosumab, on a Yellow Card

Acknowledgements

Many thanks to: Cathy Johnson, Interface Lead Pharmacist, Arden GEM Commissioning Support Unit for her help with the preparation of this *Bulletin.* Also thanks to Katherine Green, ULH Trust Lead Dietitian and Sarah Scrace, Adult Speech and Language Therapist, LCHS for their contributions to the assessment of *Thick & Easy Clear.*

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February 2016

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