NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 4 **February 2013**

What's new this month?

- **Following a review of oral mesalazine products, *Octasa 400mg MR* and *800mg MR* tablets emerge as the 400mg and 800mg formulations of choice. ULH gastroenterologists intend to initiate *Octasa* in preference to *Asacol 400mg and 800mg MR* tablets and *Ipocol* tablets 400mg in new patients. Existing patients in remission taking alternative preparations should be allowed to continue on their current treatment (see pages 3 to 7)**
- ***Mezavant XL* 1.2g tablets are similarly licensed to alternative oral mesalazine preparations, but are even higher in cost than premium price products like *Asacol 800mg MR*; they should be reserved solely for those who are likely to benefit from a simplified once daily treatment regimen (i.e. patients with adherence problems) (see pages 3 to 7)**
- **ULH gastroenterologists will continue to initiate *Pentasa* formulations, particularly within the context of the management and remission of Crohn's colitis. Where patients are initiated on *Pentasa*, they should be encouraged to participate in the free patient support programme put in place by the manufacturer (Ferring Pharmaceuticals) designed to assist the patient through the initial 180 days of treatment and to help improve compliance (see pages 3 to 7).**
- **Different mesalazine preparations cannot always be considered to be interchangeable. As a result of this, all prescribing of mesalazine preparations should clearly specify the brand name of the product prescribed. Prescribers are encouraged to review all patients currently taking mesalazine to ensure that future prescribing is brand specific (see pages 3 to 7).**
- **The *Flutter* oscillating positive expiratory pressure (PEP) device is approved for use in patients with mucus producing conditions who are insufficiently responsive to assisted controlled breathing techniques. It should only be prescribed following patient assessment and recommendation of a PEP device by a specialist respiratory physiotherapist. Designation: AMBER (see page 8).**
- **Colecalciferol 800iu tablets (*Desunin*) are designated GREEN and offer an alternative to colecalciferol 800iu capsules (*Fultium*) in the treatment of deficiency of vitamin D. *Desunin* is preferred to *Fultium* in patients with peanut allergy or in those with a dietary preference that excludes animal products (i.e. vegetarian or vegan diet) (see page 8).**
- ***Tredaptive* a combination product containing extended release nicotinic acid 1000mg and laropirant 20mg has been recalled and should no longer be prescribed. The product was licensed for the treatment of dyslipidaemia (see page 9).**
- **The MHRA has issued a new report advocating three months' supply of thyroxine tablets on repeat prescription where possible to ensure continuity of supply (see page 10).**

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This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: *JANUARY 2013 UPDATE*

Drug	Indication(s)	Traffic Light Status
Adalimumab (*Humira*) injection	For the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.	RED-RED
Bevacizumab infusion (*Avastin*)	For the first line treatment of metastatic breast cancer in combination with paclitaxel, or with capecitabine when treatment with other chemotherapy, including taxanes or anthracyclines is not appropriate	RED-RED
Colecalciferol tablets 800iu (*Desunin*)	For the prevention and treatment of vitamin D deficiency in adults and adolescents	GREEN *Desunin* is preferred to *Fultium* in patients with peanut allergy or in those with a dietary preference that excludes animal products (i.e. vegetarian or vegan diet).
Flutter oscillating positive expiratory pressure (PEP) device	For the alleviation of mucus producing conditions such as atelectasis, bronchitis, bronchiectasis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma.	AMBER - should only be prescribed following patient assessment and recommendation of a PEP device by a specialist respiratory physiotherapist.
Mesalazine (*Asacol 400mg and 800mg MR*) tablets	Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis	AMBER –should be initiated by a gastroenterologist. Shared care guideline not required. Second line choice; *Octasa MR* 400mg or 800mg preferred.
Mesalazine (*Ipocol*) 400mg tablets	Mild to moderate ulcerative colitis. Maintenance of remission of	AMBER –should be initiated by a gastroenterologist. Shared care

	ulcerative colitis.	guideline not required. Second line choice; *Octasa MR* 400mg or 800mg preferred.
Mesalazine (*Mezavant XL*)1200mg tablets	Mild to moderate ulcerative colitis. Maintenance of remission of ulcerative colitis.	AMBER –should be initiated by a gastroenterologist. Shared care guideline not required. Third line choice; *Octasa MR* 400mg or 800mg preferred.
Mesalazine (*Octasa MR)* 400mg and 800mg tablets	Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis	AMBER –should be initiated by a gastroenterologist. Shared care guideline not required. First line preferred choice
Mesalazine (*Pentasa*) Slow Release 500mg and1g tablets and 1g/2g sachets	Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis	AMBER –should be initiated by a gastroenterologist. Shared care guideline not required. Preferred choice in some contexts
Nicotinic acid 1000mg/ laropirant 20mg MR tablets (*Tredaptive*)	For the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia and in patients with primary hypercholesterolaemia	RED-RED Product recalled

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.**

REVIEW: *ORAL MESALAZINE PRODUCTS FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE*

In conjunction with the gastroenterologists at United Lincolnshire Hospitals Trust, PACEF have undertaken a full review of the range of oral mesalazine products currently in use in county for the treatment of inflammatory bowel disease. For the purposes of this review, we have divided the products into three categories:

- 400mg mesalazine formulations (*Asacol 400mg MR* tablets, *Ipocol* tablets and *Octasa 400mg MR* tablets (replacement for the recently discontinued *Mesren MR* tablets– see *PACE Bulletin* Vol 6 No 19 (December 2012)).
- 800mg mesalazine formulations (*Asacol 800mg MR* tablets and *Octasa 800mg MR* tablets (replacement for the recently discontinued *Mesren MR* tablets – see *PACE Bulletin* Vol 6 No 19 (December 2012)).
- *Pentasa* 500mg and 1g SR tablets.

National guidance and published reviews

The British Society of Gastroenterology *Guidelines for the management of Inflammatory Bowel Disease* (2011) do not differentiate between different brands of mesalazine. The guideline states that the efficacy of the various aminosalicylate formulations may depend more on patient adherence with the prescribed dose than the delivery system used. A *Drug and Therapeutics Bulletin* review published in same year supported this view and concluded that there is little difference in efficacy

between the different mesalazine products and that choice of therapy should depend on other factors such as adherence to therapy.

The therapeutic effect of mesalazine is thought to be dependent upon direct contact between the active compound with the diseased area of the gut. Therefore the site at which mesalazine is released from any particular formulation is a critical factor in determining the most suitable preparation for the individual patient.

400mg mesalazine formulations

Asacol 400mg MR tablets, *Ipocol* tablets and *Octasa 400mg MR* tablets are all similar in terms of formulation, optimal pH for drug release and site of drug release:

Table 1 – Formulation and release characteristics of MR mesalazine tablets

Drug	Formulation	Optimal drug release pH	Site of drug release
Asacol 400mg MR tablets	400mg: Enteric coated with Eudragit S	>7	Terminal ileum & large bowel (colon and rectum)
Ipocol tablets	Enteric coated with Eudragit S	>7	Terminal ileum and colon
Mesren MR 400mg tablets	Enteric coated with Eudragit S	>7	Terminal ileum and colon

Table 2 - Release characteristics of *Asacol 400mg MR*, *Ipocol* MR and *Mesren MR* tablets

	Asacol 400mg MR	Ipocol MR	Mesren MR
pH 1.0-1.2 for 2 hours	0% release	0% drug release	0% release
pH 6.4 for 1 hour	<1% released	13% – 41% released	<1% released
pH 7.2 for 1 hour	~98% released in 30 - 60 minutes	59% released in 30 - 60 minutes	~99% released in 30 - 60 minutes

N.B. pH 1.0-1.2 mimics the conditions in the stomach; pH 6.4 – 6.5 mimics the conditions in the small bowel and pH 7.2 - 7.5 mimics the conditions in the terminal ileum/colon.

Octasa 400mg MR tablets are now available and have been launched to replace the now discontinued *Mesren MR* 400mg formulation. As *Mesren MR* and *Octasa MR* are directly equivalent products, it is reasonable to assume that any reference to *Mesren MR* 400mg in the tables above applies equally to *Octasa MR* products. PACEF have assumed that all remaining patients on *Mesren MR* formulations have now been transferred over to *Octasa MR* as advised in *PACE Bulletin* Vol No 19 (December 2012)).

A cost comparison of the three products reveals the following:

Table 3

Product	Licensed indication	Dose (in divided doses unless stated.	Annual treatment costs*
Asacol 400mg MR tablets e.c.	Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis	Acute -2.4g maintenance 1.2g -2.4g	£713.68 £356.81-£713.68
Ipocol tablets 400mg e.c.	Mild to moderate ulcerative colitis. Maintenance of	Acute -2.4g maintenance 1.2g -2.4g	£757.48 £378.74-£757.48

	remission of ulcerative colitis.		
***Octasa 400mg MR* tablets e.c.**	**Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis**	**Acute -2.4g maintenance 1.2g -2.4g**	**£473.20 £236.60 -£473.20**

*price varies according to which pack size is used

PACEF Recommendation: *400mg mesalazine formulations*

PACEF accept that *Asacol 400mg MR* tablets, *Ipocol* tablets 400mg and *Octasa 400mg MR* tablets are all similar products in terms of formulation, optimal pH for drug release and site of drug release and that there is little difference in clinical efficacy or in licensed indications. However, as *Octasa 400mg MR* tablets are significantly lower in cost than the two alternatives, it is recommended that *Octasa 400mg MR* tablets should be used first-line in all new patients where the oral mesalazine 400mg strength is indicated. ULH gastroenterologists will be increasingly initiating *Octasa 400mg MR* tablets within this context. Existing patients in remission taking alternative preparations should be allowed to continue on their current treatment.

800mg mesalazine formulations

There are differences in formulation between *Asacol 800mg MR* tablets and *Octasa 800mg MR* tablets in terms of enteric coating, although this does not seem to result in any significant clinical difference between the two formulations. Once again, there seems to be very little difference in release characteristics between the two (see Table 1). *Mezavant XL* 1200mg is a once daily formulation included in the table that also emerges as broadly equivalent to the two MR 800mg products in terms of site of drug release and clinical efficacy.

Table 3 – Formulation and release characteristics of MR mesalazine tablets

Drug	Formulation	Optimal drug release pH	Site of drug release
Asacol MR	400mg: Enteric coated with Eudragit S 800mg: Enteric coated with Eudragit S and Eudragit L	>7	Terminal ileum & large bowel (colon & rectum)
Mezavant XL	1200mg: Film coated with methacrylate copolymers Type A, Type B	>7	Colon
Octasa MR	Enteric coated with Eudragit S	>7	Terminal ileum & colon

The licensed indications of *Asacol 800mg MR* tablets and *Octasa 800mg MR* tablets are detailed in Table 3 and are identical to those recorded for the 400mg MR products. Both 800mg MR tablets hold marketing authorisations for the treatment of mild to moderate acute exacerbations of ulcerative colitis and for the maintenance of remission; both are also licensed for the maintenance of remission in Crohn's ileo-colitis. There are no published studies that directly compare *Asacol 400mg* or *800mg MR* with similar *Octasa* formulations.

Evidence to support the use of *Asacol MR* comes from a series of clinical trials known as the ASCEND studies; these demonstrate that both the 2.4g and 4.8g doses improve or resolve the symptoms of mild to moderately active ulcerative colitis over a six week period. Further analysis of ASCEND data indicates that the higher

doses of mesalazine (4.8mg /day) provide numerically greater improvements in symptom control in patients with moderately active disease than the lower 2.4g dose. Results from the ASCEND 1 trial, which included patients with milder disease, suggest that there is no significant benefit from using higher doses in those with milder disease. Based on the similar formulations, identical strengths and release characteristics and in the absence of comparative data, it is reasonable to conclude that the benefits attained from using the higher dose of 4.8g of *Asacol MR* would translate over to the higher dose of the *Octasa MR* formulation.

A cost comparison of the two products, which includes *Mezavant XL* 1.2g for reference, reveals the following:

Product	**Dose (in divided doses unless stated.**	**Annual treatment costs***
Asacol 800mg MR tablets e.c.	Acute 2.4g-4.8g maintenance up to 2.4g	£713.56 -£1,427.12
Mezavant XL 1.2g tablets	2.4g – 4.8g once daily Maintenance 2.4g daily	£757.60 -£1,515.21 £757.60
***Octasa 800mg MR* tablets e.c.**	**Mild Acute 1.2g** **Moderate acute 2.4g-4.8g** **maintenance 1.6g-2.4g**	**£576.33** **£576.33- £1,152.67** **£384.22-£576.33**

*price varies according to which pack size is used

Mezavant XL 1.2g tablets hold a marketing authorisation for the treatment of 'mild to moderate ulcerative colitis' and 'maintenance of remission of ulcerative colitis'.

PACEF Recommendation: *800mg mesalazine formulations*
PACEF accept that *Asacol 800mg MR* tablets and *Octasa 800mg MR* tablets are similar products in terms of formulation, optimal pH for drug release and site of drug release. In the absence of published comparative data to the contrary, there is no evidence of significant difference in clinical efficacy and no difference in licensed indications. However, as *Octasa 800mg MR* tablets are significantly lower in cost than *Asacol 800mg MR* tablets, it is recommended that *Octasa 800mg MR* tablets should be used first-line in all new patients where the oral mesalazine 800mg strength is indicated. ULH gastroenterologists will be increasingly initiating *Octasa 800mg MR* tablets within this context. Existing patients in remission taking alternative preparations should be allowed to continue on their current treatment. In view of the superior efficacy data, the 4.8gram dose should be used in patients with moderately active disease, who can tolerate this dose to achieve rapid resolution of symptoms. *Mezavant XL* 1.2g tablets are similarly licensed, but are even higher in cost than *Asacol* 800mg. *Mezavant XL* should be reserved solely for those who are likely to benefit from a simplified once daily treatment regimen (i.e. patients with adherence problems) and should only be initiated in new patients by a gastroenterologist. The British Society of Gastroenterology guidelines highlight the importance of good patient compliance in the successful management of IBD.

***Pentasa* formulations**

Pentasa is an alternative MR mesalazine preparation, available either as an oral tablet or as granules in strengths of 500mg (tablet only) 1gram (tablet/granules) and 2 gram (tablet/granules). All formulations are licensed for the treatment of mild to moderate ulcerative colitis. *Pentasa* is a different formulation to those already reviewed and has different release characteristics as detailed below:

Drug	Formulation	Optimal drug release pH	Site of drug release
Pentasa Slow Release tablets	Ethylcellulose coated microgranules to allow slow continuous release	Enteral pH	Duodenum to rectum

Unfortunately, due to the lack of comparative data between different formulations and the very different release characteristics of the *Pentasa* range, it has not proved possible to confirm equivalence or similarity between different strengths of *Pentasa* and other oral mesalazine formulations. Nonetheless, *Pentasa* emerges from a cost comparison with other agents as lower in cost that *Asacol MR*, *Ipocol* and *Mezavant XL* and even lower cost in some scenarios than *Octasa 400mg MR* and *800mg MR.*

Product	Dose (in divided doses unless stated.	Annual treatment costs*
Octasa 400mg *MR* tablets **e.c.**	Acute -2.4g maintenance 1.2g -2.4g	£473.20 £236.60 -£473.20
Octasa 800mg MR tablets **e.c.**	Mild Acute 1.2g Moderate acute 2.4g-4.8g maintenance 1.6g-2.4g	£576.33 £576.33- £1,152.67 £384.22-£576.33
Pentasa SR tablets 500mg	**Acute up to 4g Maintenance 2g**	**£895.15 £447.57**
Pentasa SR tablets 1gram	**Acute up to 4g Maintenance 2g**	**£895.20 £447.60**
Pentasa sachets 1 gram	**Acute up to 4g Maintenance 2g**	**£895.15 £447.57**
Pentasa sachets 2 gram	**Acute up to 4g Maintenance 2g**	**£895.20 £447.60**

PACEF Recommendation: *Pentasa formulations*
Local gastroenterologists have expressed a preference to continue to initiate *Pentasa* formulations, particularly within the context of the management and remission of Crohn's colitis. Where patients are initiated on *Pentasa*, they should be encouraged to participate in the free patient support programme put in place by the manufacturer (Ferring Pharmaceuticals) designed to assist the patient through the initial 180 days of treatment and to help improve compliance.

PACEF Recommendation: *Prescribing mesalazine preparations by brand*
Different mesalazine preparations cannot always be considered to be interchangeable. As a result of this, all prescribing of mesalazine preparations should clearly specify the brand name of the product prescribed. Prescribers are encouraged to review all patients currently taking mesalazine to ensure that future prescribing is brand specific.

References
1. British Society of Gastroenterology, *Guidelines for the management of Inflammatory Bowel Disease in adults* (2011)
2. UKMI, *Medicines Questions and Answers* 67.4 What are the differences between different brands of mesalazine tablets (www.nelm.nhs.uk 6th January 2012).

NEW DEVICE ASSESSMENT: *FLUTTER OSCILLATING POSITIVE EXPIRATORY PRESSURE DEVICE*

Flutter is an oscillating positive expiratory pressure (PEP) device which may be of use in the alleviation of mucus producing conditions such as atelectasis, bronchitis, bronchiectasis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma. It is a pipe shaped device with a mouthpiece at one end and a perforated plastic cover at the other; inside is a high density steel ball which rests within a plastic circular cone. Before exhalations the steel ball blocks the conical

canal of the device. The ball is moved by a combination of the pressure of exhaled air, the force of gravity on the ball and the angle of the cone. During exhalation the steel ball rolls and bounces up and down, creating an opening and closing cycle within the valve like device which repeats many times during each exhalation. The oscillations in expiratory pressure and airflow that are created by the device result in vibrations occurring within the airways. This can be felt as a fluttering sensation, hence the name given to the device. The result of the vibrations is to loosen mucus from the airway walls. *Flutter* therapy is complete when no further mucus can be expectorated. Frequency of use and duration of each session varies with each patient, but usually the whole process takes between 5 to-15 minutes and is repeated twice daily, once in the morning and once in the late afternoon or evening.

There is very little published information on the *Flutter* device. A Cochrane review published in 2009 covering the use of oscillating devices concluded that there was no clear evidence that oscillation was more or less effective overall than other forms of physiotherapy. While oscillating devices can be effective at clearing secretions and can increase expectorated sputum volume, there is no evidence to suggest that these devices are superior to other physiotherapy techniques when improved respiratory function is used as the primary outcome.

The Cystic Fibrosis Trust have included the use of oscillating PEP devices in their standards of care and good practice for the physiotherapy management of CF. The British Thoracic Society guideline for non-CF bronchiectasis also recommends oscillating devices as adjunct interventions to active cycle breathing techniques to aid airway clearance.

A number of different oscillating PEP devices are available commercially (e.g. *Flutter*, *Acapella, Cornet*) and traditionally patients have been offered the devices on short-term loan from specialist physiotherapy services followed by encouragement to purchase their own from the manufacturer if the trial proved beneficial. The *Flutter* device is the first of the oscillating PEP devices to become available on NHS prescription; the current *Drug Tariff* price is £40.50.

PACEF Recommendation

There is evidence to suggest that oscillating PEP devices like *Flutter* are helpful in enabling patients with mucus producing conditions to clear secretions, increase expectorated sputum volume and improve respiratory function. This may, in turn, reduce the risk of respiratory infection and improve the patient's general health and wellbeing. However, oscillating PEP devices are not easy to use effectively and patients must be trained in their use by specialist physiotherapy services. The patient must also have tried and gained insufficient benefit from alternative techniques such as assisted controlled breathing (ACBT). As a result of this, the *Flutter* PEP device is designated AMBER. It should only be prescribed following patient assessment and recommendation of a PEP device by a specialist respiratory physiotherapist. It should not be prescribed in response to a direct patient request to a GP as physiotherapist assessment and training is crucial to ensure selection of appropriate patients and maximum benefit from the device.

NEW DRUG ASSESSMENT: *COLECALCIFEROL TABLETS 800 IU (DESUNIN)*

In *PACE Bulletin* Vol 6 No 14 (September 2012), we provided guidance on the treatment of vitamin D deficiency and recommended treatments and doses based upon the level of deficiency as defined in the summary table below:

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	Prescribe 60,000 units weekly of colecalciferol for 12 weeks (either as a single weekly dose or 20,000 units three times a week).
Deficiency associated with disease risk	25-50 nmol/l 25 hydroxyvitamin D	Prescribe 800-1600 units of colecalciferol daily for 12 weeks
Insufficiency	50-75nmol/l 25 hydroxyvitamin D	Consider lifestyle advice including: increased dietary intake and safe sun exposure. Refer to PACEF guidance on the prevention of vitamin D insufficiency
Replete	>75nmol/l 25 hydroxyvitamin D	No treatment necessary

Within this context, colecalciferol 800iu capsules (*Fultium*) were assessed by PACEF and approved for first line use in the management of proven vitamin D deficiency where a daily dose of between 800-1600iu colecalciferol was required.

Desunin (colecalciferol 800iu tablets) is a newly licensed colecalciferol preparation that offers an alternative option to *Fultium*. In contrast to *Fultium*, it has the advantage of not containing either arachis oil or animal sourced gelatine and provides an alternative for patients with peanut allergy or a dietary preference that excludes animal products (i.e. vegetarian or vegan diet). A cost comparison reveals that both products are the same price: £3.60 for 30.

PACEF Recommendation

Colecalciferol 800iu tablets (*Desunin*) are designated GREEN and offer an alternative to colecalciferol 800iu capsules (*Fultium*) in the treatment of deficiency of vitamin D. *Desunin* is preferred to *Fultium* in patients with peanut allergy or in those with a dietary preference that excludes animal products (i.e. vegetarian or vegan diet).

EUROPEAN MEDICINES AGENCY AND MHRA REVIEW OF THE SAFETY OF *TREDAPTIVE*

Tredaptive is a combination product containing extended release nicotinic acid 1000mg plus laropiprant 20mg; it was licensed for the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia and in patients with primary hypercholesterolaemia but has recently been recalled in a letter to healthcare professionals circulated in January 2013.

A European review of *Tredaptive* (and similar medicines available outside the UK) was started in December 2012 after new data from a large long-term study (HPS2-THRIVE) involving over 25,000 patients suggested that the benefits of these medicines did not outweigh the risks. In HPS2-THRIVE, adding *Tredaptive* to simvastatin did not provide any additional benefit in terms of reducing the risk of major vascular events (e.g. heart attack, stroke) compared to statin therapy alone. In addition, a higher risk of non-fatal, but serious, adverse events were reported

including bleeding (intracranial and gastro-intestinal), myopathy, infections and new-onset diabetes.

In December 2012, UK healthcare professionals were asked not to start any new patients on *Tredaptive*. The January 2013 letter announced that *Tredaptive* had been recalled.

PACEF Recommendation:
As a result of this product recall, nicotinic acid 1g/laropiprant 20mg MR tablets (*Tredaptive*) are designated RED-RED and should no longer be prescribed.

Reference:
MHRA *Drug Safety Update*, Vol 6 No 6 (January 2013)

MHRA REVIEW LEVOTHYROXINE TABLET SUPPLY ISSUES

In response to recent instability in the marketplace relating to supply of levothyroxine tablets and concerns over possible lack of clinical equivalence between different formulations, the MHRA have issued a report entitled *Levothyroxine Tablet Products: A Review of Clinical and Quality Considerations* (January 2013). One of the recommendations relates to prescribed quantities:

> 'Levothyroxine should be prescribed and dispensed in quantities covering three months supply, where appropriate, in order to address issues of continuity of supply and also to improve convenience to patients.'

PACEF Recommendation:
In accordance with MHRA guidance, prescribers are asked to consider prescribing 3 months' supply of levothyroxine tablets on each repeat prescription where appropriate for the individual patient. This should be seen as an exception to the established rule which is supportive of 28 day quantities on repeat for most patients.

Reference:
MHRA, *Levothyroxine Tablet Products: A Review of Clinical and Quality Considerations* (January 2013)

UPDATED SHARED CARE GUIDELINES

Revised and updated versions of the following shared care guidelines are now available:

- *Hydroxychloroquine in Rheumatology*
- *Leflunomide for the treatment of adult patients with Rheumatoid Arthritis (RA) and for treatment of active Psoriatic Arthritis (PsA)*
- *Methotrexate in Rheumatology*
- *Sulfasalazine in Rheumatology*
- *Lanthanum in the management of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis who did not respond to or were unable to tolerate treatment with sevelamer and for controlling hyperphophataemia associated with chronic kidney disease*
- *Tacrolimus for maintenance of immunosuppression after kidney transplantation in adults*

Copies are available from the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF. Further information is

available from Cathy Johnson, our Interface Lead Pharmacist (cathy.johnson@lpct.nhs.uk)

NICE TECHNOLOGY APPRAISAL 262: *ADALIMUMAB FOR THE TREATMENT OF MODERATE TO SEVERE ULCERATIVE COLITIS* (TERMINATED APPRAISAL) (JULY 2012)

NICE is unable to recommend the use in the NHS of adalimumab for the treatment of moderate to severe ulcerative colitis because no evidence submission was received from the manufacturer or sponsor of the technology.

PACEF Recommendation:
Adalimumab (*Humira*) injection is designated RED-RED for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

NICE TECHNOLOGY APPRAISAL 263: *BEVACIZUMAB IN COMBINATION WITH CAPECITABINE FOR THE FIRST-LINE TREATMENT OF METASTATIC BREAST CANCER* (AUGUST 2012)

Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months.

PACEF Recommendation:
Bevacizumab infusion (*Avastin*) is designated RED-RED for this indication. NICE have already failed to recommend bevacizumab for a range of other indications including: first-line treatment of metastatic breast cancer in combination with a taxane and for the treatment of metastatic colorectal cancer in combination with various agents.

MHRA *DRUG SAFETY UPDATE* (DECEMBER 2012)

Codeine containing pain relief for children: safety review initiated following post-surgical fatalities in ultra-rapid metabolisers

A European review of the safety of codeine containing medicines licensed for pain relief was started on October 2012 in response to concerns of an increased risk of morphine toxicity in susceptible children linked to a genetically determined higher rate of metabolism of codeine which results in higher than expected morphine blood levels. The current edition of the *BNF for Children* contains a note of caution with regard to variable metabolisers of codeine and the marked increase in side effects that can occur with rapid metabolism.

The MHRA have issued the following advice to healthcare professionals

- Clinicians should remain aware that patients may respond differently to codeine. Those caring for patients taking codeine should be advised to seek professional help if symptoms occur.

- Symptoms of codeine toxicity include reduced levels of consciousness, lack of appetite, somnolence, constipation, respiratory depression, pin-point pupils, nausea and vomiting.

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February 2013